

## ACTUALIZACIÓN 2021 DE LA GUÍA ESPAÑOLA DE LA EPOC (GesEPOC). DIAGNÓSTICO Y TRATAMIENTO DEL SÍNDROME DE AGUDIZACIÓN DE LA EPOC

### Suplemento. Preguntas PICO y evaluación de la evidencia.

#### Pregunta para responder:

#### ¿Se deben prescribir antibióticos en las agudizaciones de la EPOC?

Se identificó una revisión sistemática (RS), que incluyó 19 ensayos clínicos aleatorizados (ECAs) en pacientes EPOC y que evaluaron los efectos del tratamiento con antibióticos de las agudizaciones en el entorno ambulatorio y/o hospitalario.

Posteriormente se identificó un ECA (Vermeersch 2019) y una evaluación económica (realizada con los datos de un ECA incluido en la RS) sobre el uso de antibióticos en pacientes ambulatorios (Finch 2019).

Para el análisis se seleccionaron los 19 ECAs incluidos en la RS con un total de 2663 pacientes (11 estudios en pacientes ambulatorios, 7 estudios en pacientes hospitalarios y 1 estudio en pacientes críticos) y un estudio posterior que incluyó 301 pacientes hospitalarios. Los estudios asignaron de forma aleatoria a los pacientes a recibir placebo (en 4 estudios el grupo control recibió prednisolona) o antibióticos (amoxicilina/ácido clavulánico, trimetropin/sulfametoxazol, amoxicilina, doxiciclina, ciprofloxacina, amoxicilina/clavulanate, cefaclor, ofloxacina, penicilina via parenteral, tetraciclina, chloramfenicol, co-trimoxazol, piperacilina-sulbactam, ceftazidima, levofloxacina, azitromicina) durante 5 a 10 días.

El análisis se ha realizado con los estudios más recientes, excluyendo los estudios que evaluaron pautas o antibióticos actualmente en desuso.

#### Revisiones sistemáticas:

1. Vollenweider DJ, Frei A, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review). Cochrane Database Syst Rev. 2018;10(10):CD010257.

#### Ensayos clínicos aleatorizados:

##### A. Pacientes ambulatorios:

1. Allegra LGC, Grossi E, Pozzi E, Blasi F, Frigerio D, Nastri A, et al. The role of antibiotics in the treatment of chronic bronchitis exacerbation: follow-up of a multicenter study. Italian Journal of Chest Disease 1991;45(3):138-48.
2. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Annals of Internal Medicine 1987;106(2):196-204.
3. Berry DG, Fry J, Hindley CP. Exacerbations of chronic bronchitis treatment with oxytetracycline. Lancet 1960; 1:137-9.
4. Brusse-Keizer MG, van der Valk PD, Hendrix MG, Kerstjens HA, van der Palen J. Antibiotics in patients with a mild to moderate home-treated COPD exacerbation: the ABC trial. American Journal of Respiratory and Critical Care Medicine 2009;179: A1493.
5. Elmes PC, Fletcher CM, Dutton AA. Prophylactic use of oxytetracycline for exacerbations of chronic bronchitis. British Medical Journal 1957; 2:1272-5.
6. Fear EC, Edwards G. Antibiotic regimes in chronic bronchitis. British Journal of Diseases of the Chest 1962; 56:153-62.
7. Hassan, WA, Shalan I, Elsobhy M. Impact of antibiotics on acute exacerbations of COPD. Egyptian Journal of Chest Diseases and Tuberculosis 2015;64(3):579-85.
8. Jørgensen AF, Coolidge J, Pedersen PA, Petersen KP, WaldorG S, Widding E. Amoxicillin in treatment of acute uncomplicated exacerbations of chronic bronchitis.

A double-blind, placebo controlled multicentre study in general practice. Scandinavian Journal of Primary Health Care 1992;10(1):7-11.

9. Llor C, Moragas A, Hernandez S, Bayona C, Miravittles M. Efficacy of antibiotic therapy for acute exacerbations of mild to moderate COPD. American Journal of Respiratory and Critical Care Medicine 2012;186(8):716-23.
10. Sachs AP, Koëter GH, Groenier KH, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. Thorax 1995;50(7):758-63.
11. van Velzen P, Ter Riet G, Bresser P, Baars JJ, van den Berg BTJ, van den Berg JWK, et al. Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind placebo-controlled trial. Lancet Respiratory Medicine 2017;5(6):492-9.

#### **B. Pacientes hospitalarios:**

1. Alonso Martinez JL, Rubio Obanos MT, Samperiz Legarre AL, Escolar Castellon F, Carrasco del Amo ME. Antibiotic treatment for acute episodes of chronic obstructive pulmonary disease [Tratamiento con antibióticos de las agudizaciones de la enfermedad pulmonar obstructiva crónica]. Anales de Medicina Interna 1992;9(8):377-80.
2. Daniels JM, Snijders D, de Graaff CS, Vlaspolter F, Jansen HM, Boersma WG. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2010;181(2):150-7.
3. Manresa F, Blavia R, Martin R, Linares J, Rodriguez B, Verdaguer R. Antibiotics for exacerbations of chronic bronchitis. Lancet 1987;2(8555):394-5.
4. Petersen ES, Esmann V, Honcke P, Munkner C. A controlled study of the effect of treatment on chronic bronchitis. An evaluation using pulmonary function tests. Acta Medica Scandinavica 1967;182(3):293-305.
5. Pines A, Raafat H, Plucinski K, Greenfield JS, Solari M. Antibiotic regimens in severe and acute purulent exacerbations of chronic bronchitis. British Medical Journal 1968;2(607):735-8.
6. Pines A, Raafat H, Greenfield JS, Linsell WD, Solari ME. Antibiotic regimens in moderately ill patients with purulent exacerbations of chronic bronchitis. British Journal of Diseases of the Chest 1972;66(2):107-15.
7. Wang JX, Zhang SM, Li XH, Zhang Y, Xu ZY, Cao B. Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial. International Journal of Infectious Diseases 2016; 48:40-5.
8. Vermeersch K, Gabrovská M, Aumann J, Demedts IK, Corhay JL, Marchand E, et al. Azithromycin during Acute Chronic Obstructive Pulmonary Disease Exacerbations Requiring Hospitalization (BACE). A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial. Am J Respir Crit Care Med. 2019;200(7):857-868.

#### **C. Pacientes críticos, unidad cuidados intensivos:**

1. Noura S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet 2001;358(9298):2020-5.

#### **Evaluación económica:**

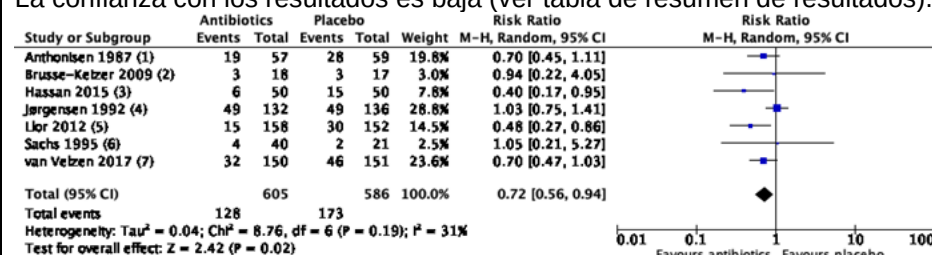
1. Finch AP, van Velzen P, Ter Riet G, Sterk PJ, Prins JM, Bosmans JE. Doxycycline Added to Prednisolone in Outpatient-Treated Acute Exacerbations of COPD: A Cost-Effectiveness Analysis Alongside a Randomised Controlled Trial. Pharmacoeconomics. 2019;37(5):689-699.

**PACIENTES AMBULATORIOS: ANTIBIÓTICOS vs PLACEBO****Fracaso terapéutico dentro de las cuatro semanas**

La definición de esta variable fue heterogénea entre los distintos estudios e incluyó la no-resolución o empeoramiento de los síntomas tras el tratamiento, muerte debido a exacerbación o necesidad de tratamiento adicional con antibióticos u otros tratamientos para la COPD.

En el análisis conjunto de los datos (7 ECAs, 1191 pacientes y 301 eventos) muestra que el tratamiento con antibióticos (amoxicilina, doxiciclina, amoxicilina/ácido clavulánico, ciprofloxacina o co-trimoxazol) reduce de forma significativa el fracaso terapéutico respecto a placebo: riesgo relativo (RR) de 0.72 (0.56 a 0.94); 83 menos por 1000 (de 130 menos a 18 menos).

La confianza con los resultados es baja (ver tabla de resumen de resultados).

**Footnotes**

- (1) within 21 days  
(2) 28 days  
(3) day 21  
(4) day 8  
(5) 20 days  
(6) failure between 4–24 days  
(7) day 21

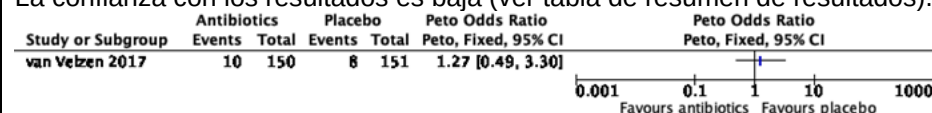
**Calidad  
baja**

**Mortalidad por cualquier causa**

Uno de los ECAs seleccionados aportó resultados para mortalidad por cualquier causa a los dos años de seguimiento.

Los resultados no muestran diferencias significativas entre el tratamiento antibiótico (doxiciclina) y placebo aunque el número de evento es muy escaso: OR 1.27 (0.49 a 3.30); 13 más por 1000 (de 26 menos a 103 más).

La confianza con los resultados es baja (ver tabla de resumen de resultados).



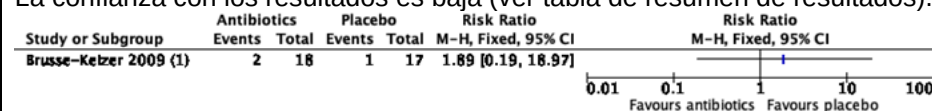
**Calidad  
baja**

**Frecuencia de agudizaciones**

Uno de los ECAs seleccionados aportó resultados para las exacerbaciones a las 4 semanas de seguimiento.

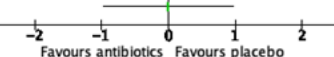
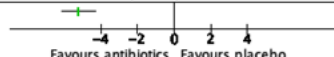
Los resultados no muestran diferencias significativas entre el tratamiento antibiótico y el placebo aunque el número de evento es muy escaso: RR 1.89 (0.19 a 18.97); 52 más por 1000 (de 48 menos a 1000 más).

La confianza con los resultados es baja (ver tabla de resumen de resultados).

**Footnotes**

- (1) relapse within 4 weeks

**Calidad  
baja**

| <b>Tiempo hasta la siguiente agudización</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |             |                     |             |         |      |         |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|---------------------|-------------|---------|------|---------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|------|----|-------|------|----|-------|------------------------|------|------|----|------|------|----|----------------------|--|---------------------|
| <p>Dos de los ECAs seleccionados evaluaron el tiempo hasta la siguiente agudización tras uno y dos años de seguimiento. Los resultados se describen por separado al no ser posible el meta-análisis de los resultados.</p> <p>En un ECA El tratamiento con antibiótico amoxicilina/ácido clavulánico mostró un incremento significativo del tiempo hasta la primera exacerbación: media 73 días más respecto al placebo; mediana 233 días (IQR 110 a 365 días) con antibióticos vs. 160 días (IQR 66 a 365 días) con placebo (<math>P=0.015</math>).</p> <p>Por el contrario, en otro ECAs el tratamiento con doxicilina no mostró diferencias frente a placebo: 148 días (IQR 95 a 200 días) vs. 161 días (IQR 118 a 211 días); (HR 1.01, 95% CI: 0.79-1.31, <math>P=0.91</math>).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p>                                                                                                                                             |             | <b>Calidad baja</b> |             |         |      |         |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| <b>Calidad de vida</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |                     |             |         |      |         |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| <p>Un ECAs que evaluó los resultados de calidad de vida (Chronic COPD Questionnaire - CCQ) no mostró diferencias significativas entre los grupos (amoxicilina/ácido clavulánico vs placebo): -2.3 (2.7) vs -2.3 (2.7); MD 0 (1.79 menos a 1.79 más alto).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p> <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">Antibiotics</th><th colspan="3">Placebo</th><th rowspan="2">Mean Difference<br/>IV, Fixed, 95% CI</th><th rowspan="2">Mean Difference<br/>IV, Fixed, 95% CI</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th></tr></thead><tbody><tr><td>Brusse-Ketzer 2009 (1)</td><td>-2.3</td><td>2.7</td><td>18</td><td>-2.3</td><td>2.7</td><td>17</td><td>0.00 [-1.79, 1.79]</td><td></td></tr></tbody></table>  <p>Footnotes<br/>(1) CCQ</p>                               |             | Study or Subgroup   | Antibiotics |         |      | Placebo |                                      |                                      | Mean Difference<br>IV, Fixed, 95% CI | Mean Difference<br>IV, Fixed, 95% CI | Mean | SD | Total | Mean | SD | Total | Brusse-Ketzer 2009 (1) | -2.3 | 2.7  | 18 | -2.3 | 2.7  | 17 | 0.00 [-1.79, 1.79]   |  | <b>Calidad baja</b> |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Antibiotics |                     |             | Placebo |      |         | Mean Difference<br>IV, Fixed, 95% CI | Mean Difference<br>IV, Fixed, 95% CI |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Mean        | SD                  | Total       | Mean    | SD   | Total   |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| Brusse-Ketzer 2009 (1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -2.3        | 2.7                 | 18          | -2.3    | 2.7  | 17      | 0.00 [-1.79, 1.79]                   |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| <b>Disnea</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |             |                     |             |         |      |         |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| <p>En uno de los ECAs seleccionados se reporta datos (35 pacientes) sobre disnea (evaluada como una de las dimensiones del Chronic Respiratory Questionnaire - CRQ) sin diferencias significativas entre los grupos (amoxicilina/ácido clavulánico vs placebo): 0.5 (1.3) vs 0.5 (1.6); MD 0 (0.97 menos a 0.97 más alto).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p> <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">Antibiotics</th><th colspan="3">Placebo</th><th rowspan="2">Mean Difference<br/>IV, Fixed, 95% CI</th><th rowspan="2">Mean Difference<br/>IV, Fixed, 95% CI</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th></tr></thead><tbody><tr><td>Brusse-Ketzer 2009</td><td>0.5</td><td>1.3</td><td>18</td><td>0.5</td><td>1.6</td><td>17</td><td>0.00 [-0.97, 0.97]</td><td></td></tr></tbody></table>  |             | Study or Subgroup   | Antibiotics |         |      | Placebo |                                      |                                      | Mean Difference<br>IV, Fixed, 95% CI | Mean Difference<br>IV, Fixed, 95% CI | Mean | SD | Total | Mean | SD | Total | Brusse-Ketzer 2009     | 0.5  | 1.3  | 18 | 0.5  | 1.6  | 17 | 0.00 [-0.97, 0.97]   |  | <b>Calidad baja</b> |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Antibiotics |                     |             | Placebo |      |         | Mean Difference<br>IV, Fixed, 95% CI | Mean Difference<br>IV, Fixed, 95% CI |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Mean        | SD                  | Total       | Mean    | SD   | Total   |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| Brusse-Ketzer 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.5         | 1.3                 | 18          | 0.5     | 1.6  | 17      | 0.00 [-0.97, 0.97]                   |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| <b>Días de baja</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |             |                     |             |         |      |         |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| <p>En uno de los ECAs evaluó los días de baja laboral. Se observó que el tratamiento con oxitetraciclina se asoció a una disminución significativa del tiempo de baja en relación con placebo: MD 5.18 menos (6.08 menos a 4.38 menos). El estudio fue realizado en 1957.</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p> <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">Antibiotics</th><th colspan="3">Placebo</th><th rowspan="2">Mean Difference<br/>IV, Fixed, 95% CI</th><th rowspan="2">Mean Difference<br/>IV, Fixed, 95% CI</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th></tr></thead><tbody><tr><td>Elmes 1957</td><td>4.25</td><td>0.96</td><td>42</td><td>9.43</td><td>2.96</td><td>46</td><td>-5.18 [-6.08, -4.28]</td><td></td></tr></tbody></table>                                                     |             | Study or Subgroup   | Antibiotics |         |      | Placebo |                                      |                                      | Mean Difference<br>IV, Fixed, 95% CI | Mean Difference<br>IV, Fixed, 95% CI | Mean | SD | Total | Mean | SD | Total | Elmes 1957             | 4.25 | 0.96 | 42 | 9.43 | 2.96 | 46 | -5.18 [-6.08, -4.28] |  | <b>Calidad baja</b> |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Antibiotics |                     |             | Placebo |      |         | Mean Difference<br>IV, Fixed, 95% CI | Mean Difference<br>IV, Fixed, 95% CI |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Mean        | SD                  | Total       | Mean    | SD   | Total   |                                      |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |
| Elmes 1957                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 4.25        | 0.96                | 42          | 9.43    | 2.96 | 46      | -5.18 [-6.08, -4.28]                 |                                      |                                      |                                      |      |    |       |      |    |       |                        |      |      |    |      |      |    |                      |  |                     |

| PACIENTES HOSPITALARIOS: ANTIBIÓTICOS vs PLACEBO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
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| <b>Fracaso terapéutico</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |                      |                   |                  |        |                                   |                                   | <b>Calidad moderada</b>      |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <b>Pacientes hospitalarios:</b><br>La definición de esta variable fue heterogénea entre los distintos estudios e incluyó la no-resolución o empeoramiento de los síntomas tras el tratamiento, muerte debido a agudización o necesidad de tratamiento adicional con antibióticos u otros tratamientos para la COPD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <br>En el análisis conjunto de los resultados (6 ECAs, 1104 pacientes y 446 eventos), el tratamiento con antibióticos muestra una reducción significativa de los fracasos terapéuticos respecto a placebo: RR 0.80 (0.68 a 0.95); 88 menos por 1000 (de 141 a 22 menos).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <br>La confianza con los resultados es moderada (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <b>Pacientes UCI:</b><br>Un ECA (93 pacientes críticos) muestra una reducción significativa del tratamiento con ofloxacino respecto a placebo: RR 0.19 (0.08 a 0.45); 458 menos por 1000 (de 520 menos a 311 menos).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <br>La confianza con los resultados es moderada (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <table><thead><tr><th>Study or Subgroup</th><th>Antibiotics<br/>Events</th><th>Antibiotics<br/>Total</th><th>Placebo<br/>Events</th><th>Placebo<br/>Total</th><th>Weight</th><th>Risk Ratio<br/>M-H, Random, 95% CI</th><th>Risk Ratio<br/>M-H, Random, 95% CI</th></tr></thead><tbody><tr><td colspan="8"><b>1.1.1 Inpatient</b></td></tr><tr><td>Wang 2016 (1)</td><td>6</td><td>95</td><td>4</td><td>96</td><td>4.6%</td><td>1.52 [0.44, 5.20]</td><td></td></tr><tr><td>Alonso Martinez 1992</td><td>4</td><td>61</td><td>6</td><td>29</td><td>4.9%</td><td>0.32 [0.10, 1.04]</td><td></td></tr><tr><td>Pines 1968</td><td>5</td><td>15</td><td>12</td><td>15</td><td>9.7%</td><td>0.42 [0.20, 0.89]</td><td></td></tr><tr><td>Daniels 2010 (2)</td><td>50</td><td>128</td><td>65</td><td>137</td><td>22.8%</td><td>0.82 [0.62, 1.09]</td><td></td></tr><tr><td>Vermeersch 2019</td><td>69</td><td>147</td><td>86</td><td>154</td><td>24.7%</td><td>0.84 [0.67, 1.05]</td><td></td></tr><tr><td>Pines 1972 (3)</td><td>93</td><td>160</td><td>46</td><td>67</td><td>25.2%</td><td>0.85 [0.69, 1.04]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>606</td><td></td><td>498</td><td>92.0%</td><td>0.80 [0.68, 0.95]</td><td></td></tr><tr><td>Total events</td><td>227</td><td></td><td>219</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="8">Heterogeneity: Tau<sup>2</sup> = 0.01; Chi<sup>2</sup> = 6.64, df = 5 (P = 0.25); I<sup>2</sup> = 25%</td></tr><tr><td colspan="8">Test for overall effect: Z = 2.51 (P = 0.01)</td></tr><tr><td colspan="8"><b>1.1.2 ICU</b></td></tr><tr><td>Nouira 2001</td><td>5</td><td>47</td><td>26</td><td>46</td><td>8.0%</td><td>0.19 [0.08, 0.45]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>47</td><td></td><td>46</td><td>8.0%</td><td>0.19 [0.08, 0.45]</td><td></td></tr><tr><td>Total events</td><td>5</td><td></td><td>26</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="8">Heterogeneity: Not applicable</td></tr><tr><td colspan="8">Test for overall effect: Z = 3.78 (P = 0.0002)</td></tr><tr><td>Total (95% CI)</td><td></td><td>653</td><td></td><td>544</td><td>100.0%</td><td>0.68 [0.51, 0.91]</td><td></td></tr><tr><td>Total events</td><td>232</td><td></td><td>245</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="8">Heterogeneity: Tau<sup>2</sup> = 0.08; Chi<sup>2</sup> = 18.20, df = 6 (P = 0.006); I<sup>2</sup> = 67%</td></tr><tr><td colspan="8">Test for overall effect: Z = 2.61 (P = 0.009)</td></tr><tr><td colspan="8">Test for subgroup differences: Chi<sup>2</sup> = 10.39, df = 1 (P = 0.001), I<sup>2</sup> = 90.4%</td></tr><tr><td colspan="8">Footnotes</td></tr><tr><td colspan="8">(1) 10 days</td></tr><tr><td colspan="8">(2) day 30</td></tr><tr><td colspan="8">(3) additional antibiotics (day 7-28)</td></tr></tbody></table> |                       |                      |                   |                  |        |                                   |                                   |                              |  | Study or Subgroup | Antibiotics<br>Events | Antibiotics<br>Total | Placebo<br>Events | Placebo<br>Total | Weight | Risk Ratio<br>M-H, Random, 95% CI | Risk Ratio<br>M-H, Random, 95% CI | <b>1.1.1 Inpatient</b> |  |  |  |  |  |  |  | Wang 2016 (1) | 6 | 95 | 4 | 96 | 4.6% | 1.52 [0.44, 5.20] |  | Alonso Martinez 1992 | 4 | 61 | 6 | 29 | 4.9% | 0.32 [0.10, 1.04] |  | Pines 1968 | 5 | 15 | 12 | 15 | 9.7% | 0.42 [0.20, 0.89] |  | Daniels 2010 (2) | 50 | 128 | 65 | 137 | 22.8% | 0.82 [0.62, 1.09] |  | Vermeersch 2019 | 69 | 147 | 86 | 154 | 24.7% | 0.84 [0.67, 1.05] |  | Pines 1972 (3) | 93 | 160 | 46 | 67 | 25.2% | 0.85 [0.69, 1.04] |  | Subtotal (95% CI) |  | 606 |  | 498 | 92.0% | 0.80 [0.68, 0.95] |  | Total events | 227 |  | 219 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 6.64, df = 5 (P = 0.25); I <sup>2</sup> = 25% |  |  |  |  |  |  |  | Test for overall effect: Z = 2.51 (P = 0.01) |  |  |  |  |  |  |  | <b>1.1.2 ICU</b> |  |  |  |  |  |  |  | Nouira 2001 | 5 | 47 | 26 | 46 | 8.0% | 0.19 [0.08, 0.45] |  | Subtotal (95% CI) |  | 47 |  | 46 | 8.0% | 0.19 [0.08, 0.45] |  | Total events | 5 |  | 26 |  |  |  |  | Heterogeneity: Not applicable |  |  |  |  |  |  |  | Test for overall effect: Z = 3.78 (P = 0.0002) |  |  |  |  |  |  |  | Total (95% CI) |  | 653 |  | 544 | 100.0% | 0.68 [0.51, 0.91] |  | Total events | 232 |  | 245 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> = 18.20, df = 6 (P = 0.006); I <sup>2</sup> = 67% |  |  |  |  |  |  |  | Test for overall effect: Z = 2.61 (P = 0.009) |  |  |  |  |  |  |  | Test for subgroup differences: Chi <sup>2</sup> = 10.39, df = 1 (P = 0.001), I <sup>2</sup> = 90.4% |  |  |  |  |  |  |  | Footnotes |  |  |  |  |  |  |  | (1) 10 days |  |  |  |  |  |  |  | (2) day 30 |  |  |  |  |  |  |  | (3) additional antibiotics (day 7-28) |  |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Antibiotics<br>Events | Antibiotics<br>Total | Placebo<br>Events | Placebo<br>Total | Weight | Risk Ratio<br>M-H, Random, 95% CI | Risk Ratio<br>M-H, Random, 95% CI |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <b>1.1.1 Inpatient</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Wang 2016 (1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 6                     | 95                   | 4                 | 96               | 4.6%   | 1.52 [0.44, 5.20]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Alonso Martinez 1992                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 4                     | 61                   | 6                 | 29               | 4.9%   | 0.32 [0.10, 1.04]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Pines 1968                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 5                     | 15                   | 12                | 15               | 9.7%   | 0.42 [0.20, 0.89]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Daniels 2010 (2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 50                    | 128                  | 65                | 137              | 22.8%  | 0.82 [0.62, 1.09]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Vermeersch 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 69                    | 147                  | 86                | 154              | 24.7%  | 0.84 [0.67, 1.05]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Pines 1972 (3)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 93                    | 160                  | 46                | 67               | 25.2%  | 0.85 [0.69, 1.04]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                       | 606                  |                   | 498              | 92.0%  | 0.80 [0.68, 0.95]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 227                   |                      | 219               |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 6.64, df = 5 (P = 0.25); I <sup>2</sup> = 25%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 2.51 (P = 0.01)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <b>1.1.2 ICU</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Nouira 2001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 5                     | 47                   | 26                | 46               | 8.0%   | 0.19 [0.08, 0.45]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                       | 47                   |                   | 46               | 8.0%   | 0.19 [0.08, 0.45]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 5                     |                      | 26                |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 3.78 (P = 0.0002)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       | 653                  |                   | 544              | 100.0% | 0.68 [0.51, 0.91]                 |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 232                   |                      | 245               |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> = 18.20, df = 6 (P = 0.006); I <sup>2</sup> = 67%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 2.61 (P = 0.009)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Test for subgroup differences: Chi <sup>2</sup> = 10.39, df = 1 (P = 0.001), I <sup>2</sup> = 90.4%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| Footnotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| (1) 10 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| (2) day 30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| (3) additional antibiotics (day 7-28)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <b>Mortalidad por cualquier causa</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <b>Pacientes hospitalarios:</b><br>El análisis conjunto de 3 ECAs (715 pacientes) no muestra una diferencia significativa entre el tratamiento con antibióticos y el placebo: OR 1.45 (0.66 a 3.17); 13 más por 1000 (de 10 menos a 59 más).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                       |                      |                   |                  |        |                                   |                                   | <b>Calidad moderada-baja</b> |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <br>La confianza con los resultados es baja (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <b>Pacientes UCI:</b><br>Un ECA (93 pacientes críticos) muestra una reducción significativa de la mortalidad asociada al tratamiento con ofloxacino respecto a placebo: OR 0.21 (0.06 a 0.72); 162 menos por 1000 (de 201 menos a 51 menos).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |
| <br>La confianza con los resultados es moderada (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |                      |                   |                  |        |                                   |                                   |                              |  |                   |                       |                      |                   |                  |        |                                   |                                   |                        |  |  |  |  |  |  |  |               |   |    |   |    |      |                   |  |                      |   |    |   |    |      |                   |  |            |   |    |    |    |      |                   |  |                  |    |     |    |     |       |                   |  |                 |    |     |    |     |       |                   |  |                |    |     |    |    |       |                   |  |                   |  |     |  |     |       |                   |  |              |     |  |     |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |                  |  |  |  |  |  |  |  |             |   |    |    |    |      |                   |  |                   |  |    |  |    |      |                   |  |              |   |  |    |  |  |  |  |                               |  |  |  |  |  |  |  |                                                |  |  |  |  |  |  |  |                |  |     |  |     |        |                   |  |              |     |  |     |  |  |  |  |                                                                                                            |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |                                                                                                     |  |  |  |  |  |  |  |           |  |  |  |  |  |  |  |             |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |                                       |  |  |  |  |  |  |  |  |  |

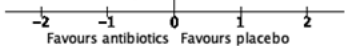
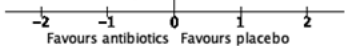
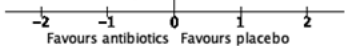
| Antibiotics                                                                |        |       |        |       |        | Placebo                                                    |                     | Peto Odds Ratio     |                     | Peto Odds Ratio     |                     |
|----------------------------------------------------------------------------|--------|-------|--------|-------|--------|------------------------------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Study or Subgroup                                                          | Events | Total | Events | Total | Weight | Peto, Fixed, 95% CI                                        | Peto, Fixed, 95% CI | Peto, Fixed, 95% CI | Peto, Fixed, 95% CI | Peto, Fixed, 95% CI | Peto, Fixed, 95% CI |
| 1.3.1 Inpatients                                                           |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| Vermeersch 2019                                                            | 3      | 147   | 6      | 154   | 24.5%  | 0.53 [0.14, 1.99]                                          |                     |                     |                     |                     |                     |
| Wang 2016                                                                  | 5      | 95    | 2      | 96    | 19.0%  | 2.45 [0.54, 11.04]                                         |                     |                     |                     |                     |                     |
| Daniels 2010                                                               | 7      | 107   | 3      | 116   | 26.8%  | 2.51 [0.71, 8.90]                                          |                     |                     |                     |                     |                     |
| Subtotal (95% CI)                                                          |        | 349   |        | 366   | 70.4%  | 1.45 [0.66, 3.17]                                          |                     |                     |                     |                     |                     |
| Total events                                                               | 15     |       | 11     |       |        |                                                            |                     |                     |                     |                     |                     |
| Heterogeneity: Chi² = 3.41, df = 2 (P = 0.18); I² = 41%                    |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| Test for overall effect: Z = 0.93 (P = 0.35)                               |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| 1.3.2 ICU patients                                                         |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| Nouira 2001                                                                | 2      | 47    | 10     | 46    | 29.6%  | 0.21 [0.06, 0.72]                                          |                     |                     |                     |                     |                     |
| Subtotal (95% CI)                                                          |        | 47    |        | 46    | 29.6%  | 0.21 [0.06, 0.72]                                          |                     |                     |                     |                     |                     |
| Total events                                                               | 2      |       | 10     |       |        |                                                            |                     |                     |                     |                     |                     |
| Heterogeneity: Not applicable                                              |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| Test for overall effect: Z = 2.50 (P = 0.01)                               |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| Total (95% CI)                                                             |        | 396   |        | 412   | 100.0% | 0.82 [0.43, 1.59]                                          |                     |                     |                     |                     |                     |
| Total events                                                               | 17     |       | 21     |       |        |                                                            |                     |                     |                     |                     |                     |
| Heterogeneity: Chi² = 10.19, df = 3 (P = 0.02); I² = 71%                   |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| Test for overall effect: Z = 0.58 (P = 0.56)                               |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
| Test for subgroup differences: Chi² = 6.78, df = 1 (P = 0.009), I² = 85.2% |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
|                                                                            |        |       |        |       |        |                                                            |                     |                     |                     |                     |                     |
|                                                                            |        |       |        |       |        | 0.001 0.1 1 10 1000<br>Favours antibiotics Favours placebo |                     |                     |                     |                     |                     |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| <p><b>Duración estancia hospitalaria</b></p> <p><b>Pacientes hospitalarios:</b><br/>Un total de 4 ECAs (601 pacientes) no muestran diferencias significativas entre el tratamiento con antibióticos y el placebo: MD 0.53 menos (2.26 menos a 1.19 más).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p> <p><b>Pacientes UCI:</b><br/>Un ECA (93 pacientes críticos) muestra una reducción significativa del tratamiento con ofloxacino respecto a placebo: MD 9.6 menos (12.84 menos a 6.36 menos).</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p> | <p><b>Calidad moderada-baja</b></p> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|

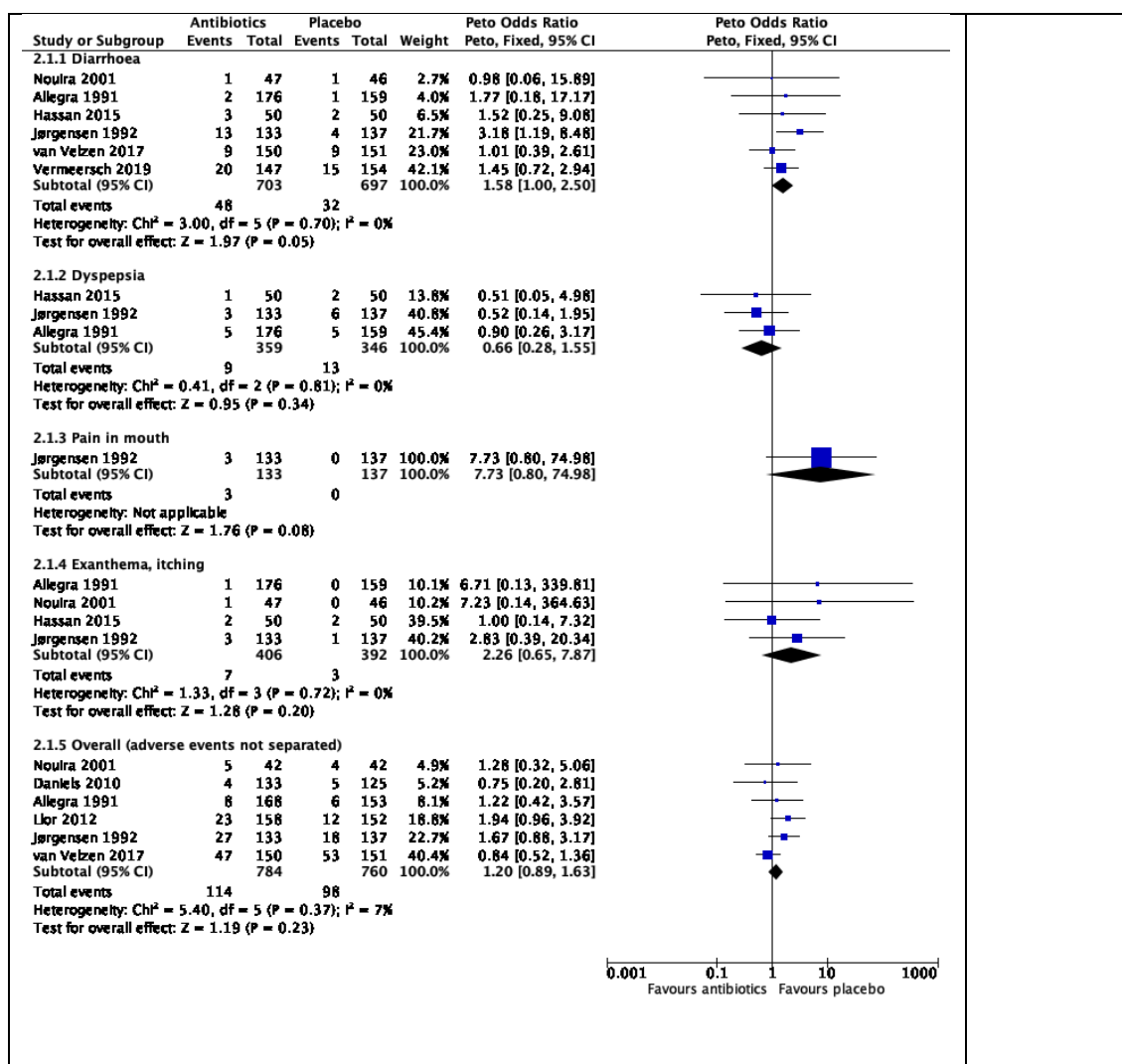
| Antibiotics                                                                   |      | Placebo |      | Mean Difference |                    | Mean Difference                                      |                    |
|-------------------------------------------------------------------------------|------|---------|------|-----------------|--------------------|------------------------------------------------------|--------------------|
| Study or Subgroup                                                             | Mean | SD      | Mean | SD              | IV, Random, 95% CI | IV, Random, 95% CI                                   | IV, Random, 95% CI |
| 1.2.1 Inpatients                                                              |      |         |      |                 |                    |                                                      |                    |
| Manresa 1987                                                                  | 12.8 | 4       | 12.3 | 4               | 14.3%              | 0.50 [-3.14, 4.14]                                   |                    |
| Vermeersch 2019                                                               | 10.7 | 8.5886  | 14.7 | 14              | 24.2%              | -3.30 [-5.48, -1.12]                                 |                    |
| Wang 2016                                                                     | 10.9 | 8.1     | 9.9  | 5.1             | 26.6%              | 1.00 [-0.92, 2.92]                                   |                    |
| Alonso Martínez 1992                                                          | 7.9  | 2.1     | 8.1  | 2.4             | 34.9%              | -0.20 [-1.22, 0.82]                                  |                    |
| Subtotal (95% CI)                                                             |      |         |      |                 | 287                | -0.53 [-2.26, 1.19]                                  |                    |
| Heterogeneity: Tau² = 1.95; Chi² = 9.19, df = 3 (P = 0.03); I² = 67%          |      |         |      |                 |                    |                                                      |                    |
| Test for overall effect: Z = 0.61 (P = 0.55)                                  |      |         |      |                 |                    |                                                      |                    |
| 1.2.2 ICU                                                                     |      |         |      |                 |                    |                                                      |                    |
| Nouira 2001                                                                   | 14.9 | 7.4     | 24.5 | 8.5             | 46                 | -9.60 [-12.84, -6.36]                                |                    |
| Subtotal (95% CI)                                                             |      |         |      |                 | 46                 | -9.60 [-12.84, -6.36]                                |                    |
| Heterogeneity: Not applicable                                                 |      |         |      |                 |                    |                                                      |                    |
| Test for overall effect: Z = 5.80 (P < 0.00001)                               |      |         |      |                 |                    |                                                      |                    |
| Test for subgroup differences: Chi² = 23.43, df = 1 (P < 0.00001), I² = 95.7% |      |         |      |                 |                    |                                                      |                    |
|                                                                               |      |         |      |                 |                    |                                                      |                    |
|                                                                               |      |         |      |                 |                    | -10 -5 0 5 10<br>Favours antibiotics Favours placebo |                    |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <p><b>Frecuencia de agudizaciones</b></p> <p>Dos ECA en pacientes hospitalizados aportan resultados de este desenlace. Los resultados se describen por separado al no ser posible el meta-análisis de los resultados.</p> <p>Un estudio que incluyó 194 pacientes no mostró diferencias significativas entre el tratamiento con antibióticos y placebo respecto al número de pacientes con agudización (RR 1,56; IC95% de 0,77 a 3,16). Un segundo estudio con 301 pacientes no mostró diferencias significativas respecto al tiempo a la primera agudización (HR 0,7; IC95% de 0,49 a 1,0).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p> | <p><b>Calidad moderada</b></p> |
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|                      |  |
|----------------------|--|
| <p><b>Disnea</b></p> |  |
|----------------------|--|

| <p>En uno de los ECAs seleccionados se reporta datos (265 pacientes) sobre disnea (evaluada como una escala de VAS de 0 a 10) sin diferencias significativas entre los grupos (doxiciclina y el placebo): MD 0.6 menos (1.27 menos a 0.07 más).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p> <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">Antibiotics</th><th colspan="3">Placebo</th><th colspan="2">Mean Difference</th><th colspan="2">Mean Difference</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th><th colspan="2">IV, Fixed, 95% CI</th><th colspan="2">IV, Fixed, 95% CI</th></tr><tr><td>Daniels 2010</td><td>-2.4</td><td>2.8</td><td>128</td><td>-1.8</td><td>2.8</td><td>137</td><td colspan="2">-0.60 [-1.27, 0.07]</td><td colspan="2"></td></tr></table> | Study or Subgroup | Antibiotics |       |      | Placebo |       |                     | Mean Difference |                                                                                    | Mean Difference |  | Mean | SD | Total | Mean | SD | Total | IV, Fixed, 95% CI |  | IV, Fixed, 95% CI |  | Daniels 2010 | -2.4 | 2.8 | 128 | -1.8 | 2.8 | 137 | -0.60 [-1.27, 0.07] |  |  |  | <b>Calidad moderada</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------|-------|------|---------|-------|---------------------|-----------------|------------------------------------------------------------------------------------|-----------------|--|------|----|-------|------|----|-------|-------------------|--|-------------------|--|--------------|------|-----|-----|------|-----|-----|---------------------|--|------------------------------------------------------------------------------------|--|-------------------------|
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                   | Antibiotics |       |      | Placebo |       |                     | Mean Difference |                                                                                    | Mean Difference |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Mean              | SD          | Total | Mean | SD      | Total | IV, Fixed, 95% CI   |                 | IV, Fixed, 95% CI                                                                  |                 |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |
| Daniels 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | -2.4              | 2.8         | 128   | -1.8 | 2.8     | 137   | -0.60 [-1.27, 0.07] |                 |  |                 |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |
| <b>PACIENTES AMBULATORIOS Y HOSPITALARIOS: ANTIBIÓTICOS vs PLACEBO</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                   |             |       |      |         |       |                     |                 |                                                                                    |                 |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |
| <b>Efectos indeseables: diarrea</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                   |             |       |      |         |       |                     |                 |                                                                                    |                 |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |
| <p>Un total de 6 ECAs (1400 pacientes y 80 eventos) muestran un aumento del número de pacientes que presentó diarrea en el grupo que recibió antibióticos [6,8% frente a 4,6%; Peto OR=1.58 (1.00 a 2.50); 25 más por 1000 (de 0 menos a 61 más)].</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                   |             |       |      |         |       |                     |                 | <b>Calidad moderada</b>                                                            |                 |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |
| <b>Cualquier efecto indeseable</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                   |             |       |      |         |       |                     |                 |                                                                                    |                 |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |
| <p>Un total de 6 ECAs (1544 pacientes y 212 eventos) muestran un aumento de los efectos indeseados en el grupo que recibió antibióticos respecto a placebo: 1.20 (0.89 a 1.63); 22 más por 1000 (de 13 menos a 65 más).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p> <p>En la siguiente figura se reportan otros efectos indeseables observados en los estudios incluidos.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                   |             |       |      |         |       |                     |                 | <b>Calidad moderada</b>                                                            |                 |  |      |    |       |      |    |       |                   |  |                   |  |              |      |     |     |      |     |     |                     |  |                                                                                    |  |                         |





## Balance entre beneficios y riesgos

### En pacientes ambulatorios:

El uso de antibióticos se asocia a una reducción de la tasa de fracasos terapéuticos, sin afectar a la calidad de vida relacionada con la salud, las recurrencias o la mortalidad. Muchas agudizaciones tratadas con placebo no se asocian con fracaso terapéutico, lo que sugiere que el antibiótico no es siempre necesario.

### En pacientes ingresados:

El uso de antibióticos se asocia a una reducción de la tasa de fracasos terapéuticos, sin reducir la duración de la estancia hospitalaria o la mortalidad.

### En pacientes ingresados en UCI:

El uso de antibióticos se asocia a una reducción significativa de la mortalidad por cualquier causa, a un menor fracaso terapéutico y una menor duración de la estancia hospitalaria.

## Calidad global de la evidencia

El grupo elaborador de la guía consideró el fracaso terapéutico y la mortalidad como desenlaces críticos para la toma de decisiones. Los otros desenlaces se consideraron importantes, pero no críticos para la toma de decisiones.

La confianza global con los resultados en pacientes EPOC ambulatorios fue BAJA principalmente debido a la variabilidad e imprecisión de los resultados.



|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <p>La confianza global con los resultados en pacientes EPOC hospitalizados fue BAJA principalmente debido a la variabilidad e imprecisión de los resultados.</p> <p>La confianza global con los resultados en pacientes EPOC ingresados en una UCI fue MODERADA principalmente debido a la imprecisión de los resultados.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| <b>Uso de recursos y costes</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |
| <p>Se encontró una evaluación económica relevante (301 pacientes ambulatorios, 2 años de seguimiento).</p> <p>En el análisis de coste utilidad, el tratamiento con doxiciclina no muestra una diferencia significativa en el valor del estado de salud (QALY) respecto a placebo: MD 0.03 (-0.00 a 0.07).</p> <p>En el análisis de coste beneficio, el tratamiento con doxiciclina no muestra una diferencia significativa en el coste total desde la perspectiva social y sistema de salud respecto a placebo: 898 € (-2617 a 4409) y 328 € (-2791 a 4409), respectivamente. Aunque la tendencia es a un mayor coste en los pacientes tratados con antibióticos. Debido a que no se realizó una búsqueda formal de la literatura se ha realizado una descripción narrativa de este estudio. La confianza en los resultados es baja debido a imprecisión.</p> |  |
| <b>Recomendaciones</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |
| <p><b>En pacientes ambulatorios:</b><br/>En los pacientes que presentan una agudización ambulatoria de la EPOC se sugiere el uso de antibióticos (recomendación débil, calidad de evidencia baja).</p> <p><b>En pacientes ingresados:</b><br/>En los pacientes que presentan una agudización de la EPOC y requieren ingreso hospitalario se sugiere el uso de antibióticos (recomendación débil, calidad de evidencia baja).</p> <p><b>En pacientes ingresados en UCI:</b><br/>Se recomienda el uso de antibióticos en todos los pacientes que presentan una agudización de la EPOC y requieren ingreso en UCI (recomendación fuerte, calidad de evidencia moderada)</p>                                                                                                                                                                                      |  |
| <b>Especificaciones</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |
| <p>Muchas de las agudizaciones tratadas con placebo no se asocian con fracaso terapéutico, lo que sugiere que el antibiótico no siempre es necesario.</p> <p>El cambio en el color del esputo (de mucoso a oscuro) se asocia con mayor aislamiento de gérmenes potencialmente patógenos por lo que se considera un parámetro útil para decidir la administración de antibióticos.</p> <p>Los pacientes que precisan soporte ventilatorio tienen mayor riesgo de infección bacteriana. En estas circunstancias se aconseja el empleo de antibióticos.</p>                                                                                                                                                                                                                                                                                                      |  |

Pregunta: ANTIBIÓTICOS vs PLACEBO en agudizaciones de EPOC; PACIENTES AMBULATORIOS

| Certainty assessment                       |                    |                 |                    |                     |                        |                       | Nº de pacientes                                                                                                                                                                                                                                                                  |                 | Efecto                 |                                                                                            | Certainty                                                                                  | Importancia |
|--------------------------------------------|--------------------|-----------------|--------------------|---------------------|------------------------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------|
| Nº de estudios                             | Diseño de estudio  | Riesgo de sesgo | Inconsistencia     | Evidencia indirecta | Imprecisión            | Otras consideraciones | Antibiotics                                                                                                                                                                                                                                                                      | placebo         | Relativo (95% CI)      | Absoluto (95% CI)                                                                          |                                                                                            |             |
| Fracaso terapéutico                        |                    |                 |                    |                     |                        |                       |                                                                                                                                                                                                                                                                                  |                 |                        |                                                                                            |                                                                                            |             |
| 7                                          | ensayos aleatorios | no es serio     | serio <sup>a</sup> | no es serio         | serio <sup>b</sup>     | ninguno               | 128/605 (21.2%)                                                                                                                                                                                                                                                                  | 173/586 (29.5%) | RR 0.72 (0.56 a 0.94)  | 83 menos por 1,000 (de 130 menos a 18 menos )                                              |  BAJA   | CRÍTICO     |
| Mortalidad por cualquier causa             |                    |                 |                    |                     |                        |                       |                                                                                                                                                                                                                                                                                  |                 |                        |                                                                                            |                                                                                            |             |
| 1                                          | ensayos aleatorios | no es serio     | no es serio        | no es serio         | muy serio <sup>c</sup> | ninguno               | 10/150 (6.7%)                                                                                                                                                                                                                                                                    | 8/151 (5.3%)    | OR 1.27 (0.49 a 3.30)  | 13 más por 1,000 (de 26 menos a 103 más )                                                  |  BAJA   | CRÍTICO     |
| Frecuencia de exacerbaciones/agudizaciones |                    |                 |                    |                     |                        |                       |                                                                                                                                                                                                                                                                                  |                 |                        |                                                                                            |                                                                                            |             |
| 1                                          | ensayos aleatorios | no es serio     | no es serio        | no es serio         | muy serio <sup>c</sup> | ninguno               | 2/18 (11.1%)                                                                                                                                                                                                                                                                     | 1/17 (5.9%)     | RR 1.89 (0.19 a 18.97) | 52 más por 1,000 (de 48 menos a 1,000 más )                                                |  BAJA   | IMPORTANTE  |
| Tiempo hasta la siguiente exacerbación     |                    |                 |                    |                     |                        |                       |                                                                                                                                                                                                                                                                                  |                 |                        |                                                                                            |                                                                                            |             |
| 2                                          | ensayos aleatorios | no es serio     | serio <sup>d</sup> | no es serio         | serio <sup>e</sup>     | ninguno               | Resultados de dos estudios:<br>mediana 233 días (IQR 110 a 365 días) con antibióticos vs. 160 días (IQR 66 a 365 días) con placebo ( <i>P</i> =0.015).<br>mediana 148 días (IQR 95 a 200 días) con antibióticos vs. 161 días (IQR 118 a 211 días) con placebo ( <i>P</i> =0.91). |                 |                        |  BAJA | IMPORTANTE                                                                                 |             |
| Calidad de vida                            |                    |                 |                    |                     |                        |                       |                                                                                                                                                                                                                                                                                  |                 |                        |                                                                                            |                                                                                            |             |
| 1                                          | ensayos aleatorios | no es serio     | no es serio        | no es serio         | muy serio <sup>f</sup> | ninguno               | 18                                                                                                                                                                                                                                                                               | 17              | -                      | MD 0 (1.79 menos a 1.79 más )                                                              |  BAJA | IMPORTANTE  |
| Disnea                                     |                    |                 |                    |                     |                        |                       |                                                                                                                                                                                                                                                                                  |                 |                        |                                                                                            |                                                                                            |             |
| 1                                          | ensayos aleatorios | no es serio     | no es serio        | no es serio         | muy serio <sup>f</sup> | ninguno               | 18                                                                                                                                                                                                                                                                               | 17              | -                      | MD 0 (0.97 menos a 0.97 más )                                                              |  BAJA | IMPORTANTE  |

| Certainty assessment |                    |                 |                |                     |             |                       | № de pacientes |         | Efecto            |                                          | Certainty                                                                                   | Importancia |
|----------------------|--------------------|-----------------|----------------|---------------------|-------------|-----------------------|----------------|---------|-------------------|------------------------------------------|---------------------------------------------------------------------------------------------|-------------|
| № de estudios        | Diseño de estudio  | Riesgo de sesgo | Inconsistencia | Evidencia indirecta | Imprecisión | Otras consideraciones | Antibiotics    | placebo | Relativo (95% CI) | Absoluto (95% CI)                        |                                                                                             |             |
| Días de baja         |                    |                 |                |                     |             |                       |                |         |                   |                                          |                                                                                             |             |
| 1                    | ensayos aleatorios | no es serio     | no es serio    | Muy serio 9         | no es serio | ninguno               | 42             | 46      | -                 | MD 5.18 menos (6.08 menos a 4.28 menos ) | <br>BAJA | IMPORTANTE  |

CI: Intervalo de confianza; RR: Razón de riesgo; OR: Odds ratio; MD: Diferencia media

### Explicaciones

- a. Variabilidad significativa en los resultados de los diferentes estudios
- b. Resultados imprecisos que no excluyen una reducción clínicamente no relevante
- c. Número de eventos muy escaso, los resultados pueden incluir un efecto importante favorable o perjudicial.
- d. Dos estudios con resultados inconsistentes.
- e. No ha sido posible analizar conjuntamente los resultados de dos estudios que muestran un beneficio relevante o no diferencias
- f. El resultado incluye un probable efecto beneficioso o perjudicial
- g. Desenlace subrogado de otros desenlaces clínicamente relevantes; el estudio aporta resultados del año 1957 con un antibiótico actualmente en desuso.

Pregunta: ANTIBIÓTICOS vs PLACEBO en agudizaciones de EPOC; PACIENTES HOSPITALARIOS

| Certainty assessment                                                  |                    |                 |                    |                     |                    |                       | Nº de pacientes |                 | Efecto                |                                                 | Certainty                                                                                        | Importancia |
|-----------------------------------------------------------------------|--------------------|-----------------|--------------------|---------------------|--------------------|-----------------------|-----------------|-----------------|-----------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------|
| Nº de estudios                                                        | Diseño de estudio  | Riesgo de sesgo | Inconsistencia     | Evidencia indirecta | Imprecisión        | Otras consideraciones | Antibiotics     | placebo         | Relativo (95% CI)     | Absoluto (95% CI)                               |                                                                                                  |             |
| Fracaso terapéutico - pacientes hospitalarios                         |                    |                 |                    |                     |                    |                       |                 |                 |                       |                                                 |                                                                                                  |             |
| 6                                                                     | ensayos aleatorios | no es serio     | no es serio        | no es serio         | serio <sup>a</sup> | ninguno               | 227/606 (37.5%) | 219/498 (44.0%) | RR 0.80 (0.68 a 0.95) | 88 menos por 1,000 (de 141 menos a 22 menos )   | <br>MODERADA  | CRÍTICO     |
| Fracaso terapéutico - pacientes en UCI                                |                    |                 |                    |                     |                    |                       |                 |                 |                       |                                                 |                                                                                                  |             |
| 1                                                                     | ensayos aleatorios | no es serio     | no es serio        | no es serio         | serio <sup>b</sup> | ninguno               | 5/47 (10.6%)    | 26/46 (56.5%)   | RR 0.19 (0.08 a 0.45) | 458 menos por 1,000 (de 520 menos a 311 menos ) | <br>MODERADA  | CRÍTICO     |
| Mortalidad por cualquier causa - pacientes hospitalarios              |                    |                 |                    |                     |                    |                       |                 |                 |                       |                                                 |                                                                                                  |             |
| 3                                                                     | ensayos aleatorios | no es serio     | serio <sup>c</sup> | no es serio         | serio <sup>d</sup> | ninguno               | 15/349 (4.3%)   | 11/366 (3.0%)   | OR 1.45 (0.66 a 3.17) | 13 más por 1,000 (de 10 menos a 59 más )        | <br>BAJA      | CRÍTICO     |
| Mortalidad por cualquier causa - pacientes en UCI                     |                    |                 |                    |                     |                    |                       |                 |                 |                       |                                                 |                                                                                                  |             |
| 1                                                                     | ensayos aleatorios | no es serio     | no es serio        | no es serio         | serio <sup>b</sup> | ninguno               | 2/47 (4.3%)     | 10/46 (21.7%)   | OR 0.21 (0.06 a 0.72) | 162 menos por 1,000 (de 201 menos a 51 menos )  | <br>MODERADA | CRÍTICO     |
| Duración de la estancia hospitalaria (días) - pacientes hospitalarios |                    |                 |                    |                     |                    |                       |                 |                 |                       |                                                 |                                                                                                  |             |
| 4                                                                     | ensayos aleatorios | no es serio     | serio <sup>c</sup> | no es serio         | serio <sup>a</sup> | ninguno               | 314             | 287             | -                     | MD 0.53 menos (2.26 menos a 1.19 más )          | <br>BAJA    | IMPORTANTE  |

Duración de la estancia hospitalaria (días) - pacientes en ICU

| Certainty assessment                       |                    |                 |                    |                     |                    |                       | № de pacientes                                                                                                                                                                                                                                                                                                                                          |         | Efecto            |                                          | Certainty        | Importancia |
|--------------------------------------------|--------------------|-----------------|--------------------|---------------------|--------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------|------------------------------------------|------------------|-------------|
| № de estudios                              | Diseño de estudio  | Riesgo de sesgo | Inconsistencia     | Evidencia indirecta | Imprecisión        | Otras consideraciones | Antibiotics                                                                                                                                                                                                                                                                                                                                             | placebo | Relativo (95% CI) | Absoluto (95% CI)                        |                  |             |
| 1                                          | ensayos aleatorios | no es serio     | no es serio        | no es serio         | serio <sup>a</sup> | ninguno               | 47                                                                                                                                                                                                                                                                                                                                                      | 46      | -                 | MD 9.6 menos (12.84 menos a 6.36 menos ) | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Frecuencia de exacerbaciones/agudizaciones |                    |                 |                    |                     |                    |                       |                                                                                                                                                                                                                                                                                                                                                         |         |                   |                                          |                  |             |
| 2                                          | ensayos aleatorios | no es serio     | serio <sup>c</sup> | no es serio         | no es serio        | ninguno               | Un estudio que incluyó 194 pacientes no mostró diferencias significativas entre el tratamiento con antibióticos y placebo (RR 1,56; IC95% de 0,77 a 3,16)<br>Un estudio reciente que incluyó 301 pacientes muestra una reducción en la tasa de nuevas exacerbaciones entre los dos grupos, al margen de la significación (HR 0,7; IC95% de 0,49 a 1,0). |         |                   |                                          | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Disnea                                     |                    |                 |                    |                     |                    |                       |                                                                                                                                                                                                                                                                                                                                                         |         |                   |                                          |                  |             |
| 1                                          | ensayos aleatorios | no es serio     | no es serio        | no es serio         | serio <sup>a</sup> | ninguno               | 128                                                                                                                                                                                                                                                                                                                                                     | 137     | -                 | MD 0.6 menos (1.27 menos a 0.07 más )    | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |

CI: Intervalo de confianza ; RR: Razón de riesgo; MD: Diferencia media; OR: Odds ratio

Explicaciones

- a. El límite superior del IC 95% de los efectos absolutos no excluye un efecto clínicamente no relevante
- b. Aunque el tamaño del efecto es grande, el número de eventos es muy escaso
- c. Variabilidad importante de los resultados entre los distintos estudios
- d. Número escaso de eventos; los límites superior e inferior del IC95% incluyen un efecto beneficioso o perjudicial clínicamente relevante

Pregunta: ANTIBIÓTICOS vs PLACEBO en agudizaciones de EPOC; PACIENTES AMBULATORIOS Y HOSPITALARIOS

| Certainty assessment          |                    |                 |                |                     |                    |                       | Nº de pacientes |                | Efecto                |                                          | Certainty                                                                                       | Importancia |
|-------------------------------|--------------------|-----------------|----------------|---------------------|--------------------|-----------------------|-----------------|----------------|-----------------------|------------------------------------------|-------------------------------------------------------------------------------------------------|-------------|
| Nº de estudios                | Diseño de estudio  | Riesgo de sesgo | Inconsistencia | Evidencia indirecta | Imprecisión        | Otras consideraciones | Antibiotics     | placebo        | Relativo (95% CI)     | Absoluto (95% CI)                        |                                                                                                 |             |
| Efectos indeseables – diarrea |                    |                 |                |                     |                    |                       |                 |                |                       |                                          |                                                                                                 |             |
| 6                             | ensayos aleatorios | no es serio     | no es serio    | no es serio         | serio <sup>a</sup> | ninguno               | 48/703 (6.8%)   | 32/697 (4.6%)  | OR 1.58 (1.00 a 2.50) | 25 más por 1,000 (de 0 menos a 61 más )  | <br>MODERADA | IMPORTANTE  |
| Cualquier efecto indeseable   |                    |                 |                |                     |                    |                       |                 |                |                       |                                          |                                                                                                 |             |
| 6                             | ensayos aleatorios | no es serio     | no es serio    | no es serio         | serio <sup>b</sup> | ninguno               | 114/784 (14.5%) | 98/760 (12.9%) | OR 1.20 (0.89 a 1.63) | 22 más por 1,000 (de 13 menos a 65 más ) | <br>MODERADA | IMPORTANTE  |

CI: Intervalo de confianza; OR: Odds Ratio

Explicaciones

- a. El límite inferior del IC95% no descarta el efecto nulo
- b. Los límites del IC95% incluyen un efecto beneficioso o perjudicial

## PREGUNTA 2

### Pregunta para responder:

**¿La presencia de un cambio en el color del esputo, es útil para guiar la administración de antibióticos en los pacientes con una agudización de la EPOC?**

No se identificó ningún ensayo clínico aleatorizado que respondiera directamente a la pregunta de interés.

Se identificó una revisión sistemática (RS) que evalúa el valor predictivo de la determinación subjetiva del cambio en el color del esputo para identificar la presencia de bacterias potencialmente patógenas en el cultivo de esputo (Chen 2020).

Aunque la RS aporta resultados sobre un desenlace subrogado (predicción de positividad del esputo), se decidió incluir esta RS y analizar los desenlaces relevantes evaluados en los estudios identificados en esta revisión.

La RS de Chen 2020 incluyó 6 estudios observacionales. No se identificó ningún estudio adicional entre la lista de referencias excluidas en la RS de Chen 2020 o en una actualización de la búsqueda hasta la fecha.

Todos los estudios incluyeron pacientes con síntomas compatibles con una agudización de la EPOC atendidos en un servicio de urgencias (de atención primaria u hospitalaria). La evaluación de la purulencia del esputo fue subjetiva por parte del clínico (en base a una escala de color) o auto reportada por el paciente en base a un cambio a una coloración amarilla-verdosa. Las bacterias potencialmente patógenas identificadas fueron heterogéneas, así como los criterios y métodos de cultivo utilizados.

Dos estudios (Soler 2012, Stockley 2000) aportaron información sobre desenlaces clínicos de interés, además del valor predictivo a partir del seguimiento clínico de los pacientes tras recibir tratamiento antibiótico según el resultado de la evaluación del esputo.

### Estudios incluidos:

1. Chen K, Pleasants KA, Pleasants RA, Beiko T, Washburn RG, Yu Z, Zhai S, Drummond MB. A Systematic Review and Meta-Analysis of Sputum Purulence to Predict Bacterial Infection in COPD Exacerbations. COPD. 2020 Jun;17(3):311-317.
2. Allegra L, Blasi F, Diano P, et al. Sputum color as a marker of acute bacterial exacerbations of chronic obstructive pulmonary disease. Respir Med. 2005;99(6):742-747.
3. Daniels JM, de Graaff CS, Vlasploder F, et al. Sputum colour reported by patients is not a reliable marker of the presence of bacteria in acute exacerbations of chronic obstructive pulmonary disease. Clin Microbiol Infect. 2010;16(6):583-588.
4. Soler N, Agusti C, Angrill J, et al. Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. Thorax. 2007;62(1):29-35.
5. Soler N, Esperatti M, Ewig S, et al. Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD. Eur Respir J. 2012;40(6):1344-1353.
6. Stockley RA, O'Brien C, Pye A, et al. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest. 2000;117(6):1638-1645.
7. Tsimogianni AM, Papiris SA, Kanavaki S, et al. Predictors of positive sputum cultures in exacerbations of chronic obstructive pulmonary disease. Respirology. 2009;14(8):1114-1120.

### Asociación entre cambio de color del esputo (valoración subjetiva) e identificación de bacterias potencialmente patógenas

Se han identificado un total de 6 estudios observacionales que analizó un total de 1092 muestras de esputo.

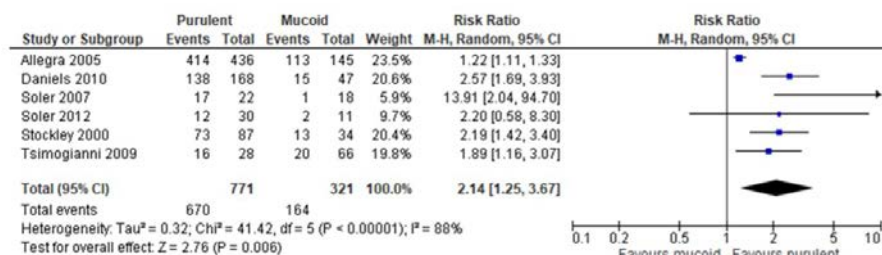
**Calidad  
muy baja**



Los resultados muestran una relación significativa entre un esputo purulento y la identificación de bacterias potencialmente patógenas. En comparación a un esputo de aspecto mucoso, un esputo purulento tiene más probabilidades de presentar un cultivo positivo: RR=2.14, IC95% de 1.25 a 3.67

Estos resultados representan los datos crudos sin ajustar. Sólo un estudio (Tsimogianni 2002) presentó los resultados ajustados por factores de riesgo. En este estudio la purulencia del esputo se asoció a un cultivo positivo de forma significativa; OR= 3.403, IC95% de 1.233 a 9.389

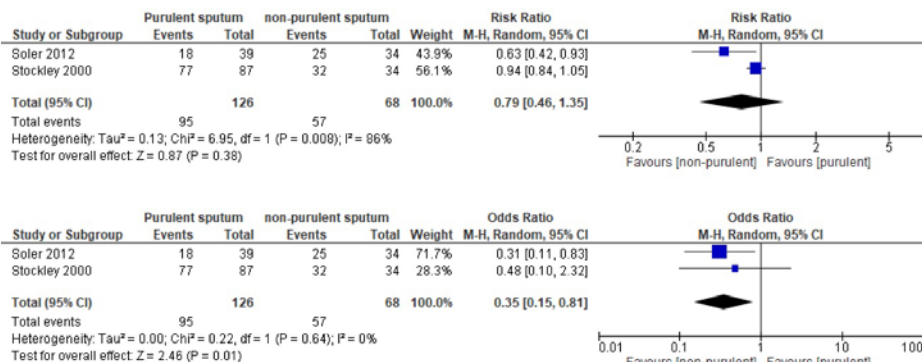
La confianza de los resultados es baja debido a las limitaciones de los estudios incluidos, la variabilidad de los resultados y los resultados indirectos.



### Curación clínica (resolución completa de los síntomas)

Se han identificado un total de 2 estudios observacionales (Soler 2012, Stockley 2000). De forma general la presencia de un esputo de aspecto purulento se asoció a un menor porcentaje de resolución completa de los síntomas. Los resultados fueron variables según se considere el análisis por riesgos relativos u odds ratio (OR=0.35 IC95% de 0.15 a 0.81; RR= 0.79 IC95% de 0.46 a 1.35).

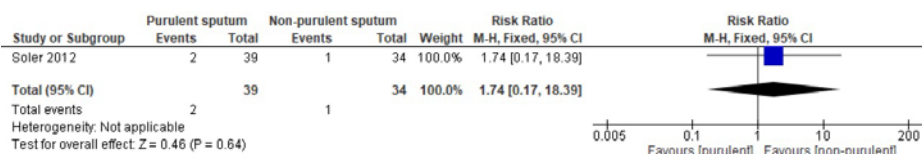
El estudio de Soler 2012 no mostró diferencias significativas de mejoría clínica entre los dos tipos de esputo a día 3 o día 30 de seguimiento, mostrando mejoría clínica en más del 90% de los casos en cualquier grupo.



**Calidad muy baja**

### Mortalidad

Se identificó un solo estudio observacional que evaluó 73 pacientes (Soler 2012). No se observan diferencias entre los tipos de esputo respecto a la mortalidad aunque el número de eventos es muy escaso (2 en los pacientes con esputo purulento; 1 en los pacientes con esputo mucoso) (RR= 1.74, IC95% de 0.17 a 18.39)



**Calidad muy baja**

### Recaídas (nuevas agudizaciones)

| Se identificó un solo estudio observacional que evaluó 73 pacientes (Soler 2012). No se observan diferencias entre los tipos de esputo respecto a la recurrencia de exacerbación a los 30 días aunque el número de eventos es muy escaso (8 en los pacientes con esputo purulento; 7 en los pacientes con esputo mucoide) (RR= 1.00, IC95% de 0.40 a 2.46)                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                 | Calidad muy baja  |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------------------|---------------------|---------------------|---------------------|---------------------|--------------------|---------------------|--------------------|-----------------|-------|--------|-------|--------------------|--------------------|------------|-------|--------------------|--------------------|------------|--------|-------------------|----|----------------|---|----|--------|---------------------|--------|-------------------|--------------|---|----|---|--|----|--------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--|--|--|--|--|--|--|--|--|
| <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Purulent sputum</th><th colspan="2">Non-purulent sputum</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Fixed, 95% CI</th><th>M-H, Fixed, 95% CI</th></tr></thead><tbody><tr><td>Soler 2012</td><td>8</td><td>39</td><td>7</td><td>34</td><td>100.0%</td><td>1.00 [0.40, 2.46]</td><td rowspan="4"></td></tr><tr><td>Total (95% CI)</td><td></td><td>39</td><td></td><td>34</td><td>100.0%</td><td>1.00 [0.40, 2.46]</td></tr><tr><td>Total events</td><td>8</td><td></td><td>7</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable<br/>Test for overall effect: Z = 0.01 (P = 0.99)</td></tr></tbody></table> |                 | Study or Subgroup | Purulent sputum     |                     | Non-purulent sputum |                     | Weight             | Risk Ratio          |                    | Events          | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | Soler 2012 | 8     | 39                 | 7                  | 34         | 100.0% | 1.00 [0.40, 2.46] |    | Total (95% CI) |   | 39 |        | 34                  | 100.0% | 1.00 [0.40, 2.46] | Total events | 8 |    | 7 |  |    |        | Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.01 (P = 0.99) |                                                                               |  |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Purulent sputum |                   | Non-purulent sputum |                     | Weight              | Risk Ratio          |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Events          | Total             | Events              | Total               |                     | M-H, Fixed, 95% CI  | M-H, Fixed, 95% CI |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Soler 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 8               | 39                | 7                   | 34                  | 100.0%              | 1.00 [0.40, 2.46]   |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                 | 39                |                     | 34                  | 100.0%              | 1.00 [0.40, 2.46]   |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 8               |                   | 7                   |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.01 (P = 0.99)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <b>Reingreso</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Se identificó un solo estudio observacional que evaluó 73 pacientes (Soler 2012). No se observan diferencias entre los tipos de esputo respecto a la re-hospitalización a los 30 días aunque el número de eventos es muy escaso (4 en los pacientes con esputo purulento; 5 en los pacientes con esputo mucoide) (RR= 0.70, IC95% de 0.20 a 2.39).                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                 | Calidad muy baja  |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Purulent sputum</th><th colspan="2">Non-purulent sputum</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Fixed, 95% CI</th><th>M-H, Fixed, 95% CI</th></tr></thead><tbody><tr><td>Soler 2012</td><td>4</td><td>39</td><td>5</td><td>34</td><td>100.0%</td><td>0.70 [0.20, 2.39]</td><td rowspan="4"></td></tr><tr><td>Total (95% CI)</td><td></td><td>39</td><td></td><td>34</td><td>100.0%</td><td>0.70 [0.20, 2.39]</td></tr><tr><td>Total events</td><td>4</td><td></td><td>5</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable<br/>Test for overall effect: Z = 0.57 (P = 0.57)</td></tr></tbody></table> |                 | Study or Subgroup | Purulent sputum     |                     | Non-purulent sputum |                     | Weight             | Risk Ratio          |                    | Events          | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | Soler 2012 | 4     | 39                 | 5                  | 34         | 100.0% | 0.70 [0.20, 2.39] |    | Total (95% CI) |   | 39 |        | 34                  | 100.0% | 0.70 [0.20, 2.39] | Total events | 4 |    | 5 |  |    |        | Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.57 (P = 0.57) |                                                                               |  |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Purulent sputum |                   | Non-purulent sputum |                     | Weight              | Risk Ratio          |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Events          | Total             | Events              | Total               |                     | M-H, Fixed, 95% CI  | M-H, Fixed, 95% CI |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Soler 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 4               | 39                | 5                   | 34                  | 100.0%              | 0.70 [0.20, 2.39]   |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                 | 39                |                     | 34                  | 100.0%              | 0.70 [0.20, 2.39]   |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 4               |                   | 5                   |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.57 (P = 0.57)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <b>Duración de la hospitalización (primera agudización)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Se identificó un solo estudio observacional que evaluó 73 pacientes (Soler 2012). No se observan diferencias entre los tipos de esputo respecto a la duración de la estancia hospitalaria de la primera agudización.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                 | Calidad muy baja  |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">Purulent sputum</th><th colspan="3">Non-purulent sputum</th><th rowspan="2">Weight</th><th colspan="2">Mean Difference</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th><th>IV, Random, 95% CI</th><th>IV, Random, 95% CI</th></tr></thead><tbody><tr><td>Soler 2012</td><td>5.9</td><td>2.3</td><td>39</td><td>6.1</td><td>4</td><td>34</td><td>100.0%</td><td>-0.20 [-1.73, 1.33]</td><td rowspan="4"></td></tr><tr><td>Total (95% CI)</td><td></td><td></td><td>39</td><td></td><td></td><td>34</td><td>100.0%</td><td>-0.20 [-1.73, 1.33]</td></tr><tr><td colspan="9">Heterogeneity: Not applicable<br/>Test for overall effect: Z = 0.26 (P = 0.80)</td></tr></tbody></table>                |                 | Study or Subgroup | Purulent sputum     |                     |                     | Non-purulent sputum |                    |                     | Weight             | Mean Difference |       | Mean   | SD    | Total              | Mean               | SD         | Total | IV, Random, 95% CI | IV, Random, 95% CI | Soler 2012 | 5.9    | 2.3               | 39 | 6.1            | 4 | 34 | 100.0% | -0.20 [-1.73, 1.33] |        | Total (95% CI)    |              |   | 39 |   |  | 34 | 100.0% | -0.20 [-1.73, 1.33]                                                           | Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.26 (P = 0.80) |  |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Purulent sputum |                   |                     | Non-purulent sputum |                     |                     | Weight             | Mean Difference     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Mean            | SD                | Total               | Mean                | SD                  | Total               |                    | IV, Random, 95% CI  | IV, Random, 95% CI |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Soler 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 5.9             | 2.3               | 39                  | 6.1                 | 4                   | 34                  | 100.0%             | -0.20 [-1.73, 1.33] |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                 |                   | 39                  |                     |                     | 34                  | 100.0%             | -0.20 [-1.73, 1.33] |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.26 (P = 0.80)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <b>Balance entre beneficios y riesgos</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| La determinación subjetiva de un cambio en el color del esputo en pacientes con una agudización de la EPOC se asoció a una mayor identificación de bacterias potencialmente patógenas.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Se trata de una prueba que no es invasiva, fácil de aplicar y sin coste alguno. En un escenario en que no se puedan aplicar otras determinaciones por falta de accesibilidad o tiempo, la valoración del cambio en el color del esputo podría tener un balance favorable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <b>Calidad global de la evidencia</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| La confianza global con los resultados es MUY BAJA debido a que se incluyeron estudios con un diseño observacional y los resultados se presentan no ajustados por los principales factores de confusión. Debido al escaso número de pacientes y eventos incluidos, algunos de los resultados son también imprecisos.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <b>Uso de recursos y costes</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| No se identificó ninguna referencia relevante para esta pregunta, aunque se trata de una prueba sin coste alguno.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| <b>Recomendaciones</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |
| Se sugiere el uso de antibióticos ante la presencia de un cambio en el color del esputo (de mucoso a oscuro) en los pacientes con una agudización de la EPOC. (recomendación débil, calidad de evidencia muy baja).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                 |                   |                     |                     |                     |                     |                    |                     |                    |                 |       |        |       |                    |                    |            |       |                    |                    |            |        |                   |    |                |   |    |        |                     |        |                   |              |   |    |   |  |    |        |                                                                               |                                                                               |  |  |  |  |  |  |  |  |  |

Pregunta: La evaluación del esputo comparado con criterio clínico habitual para guiar el tratamiento con antibiótico en las agudizaciones de la EPOC

| Certainty assessment                                      |                          |                    |                    |                     |                    |                       | Nº de pacientes          |                           | Efecto                 |                                              | Certainty         | Importancia |
|-----------------------------------------------------------|--------------------------|--------------------|--------------------|---------------------|--------------------|-----------------------|--------------------------|---------------------------|------------------------|----------------------------------------------|-------------------|-------------|
| Nº de estudios                                            | Diseño de estudio        | Riesgo de sesgo    | Inconsistencia     | Evidencia indirecta | Imprecisión        | Otras consideraciones | la evaluación del esputo | criterio clínico habitual | Relativo (95% CI)      | Absoluto (95% CI)                            |                   |             |
| Curación clínica (resolución completa de los síntomas)    |                          |                    |                    |                     |                    |                       |                          |                           |                        |                                              |                   |             |
| 2                                                         | estudios observacionales | serio <sup>a</sup> | serio <sup>b</sup> | no es serio         | no es serio        | ninguno               | 95/126 (75.4%)           | 57/68 (83.8%)             | RR 0.79 (0.46 a 1.35)  | 176 menos por 1000 (de 453 menos a 293 más ) | ⊕○○○○<br>MUY BAJA | CRÍTICO     |
| Mortalidad global                                         |                          |                    |                    |                     |                    |                       |                          |                           |                        |                                              |                   |             |
| 1                                                         | estudios observacionales | serio <sup>c</sup> | no es serio        | no es serio         | serio <sup>d</sup> | ninguno               | 2/39 (5.1%)              | 1/34 (2.9%)               | RR 1.74 (0.17 a 18.39) | 22 más por 1000 (de 24 menos a 511 más )     | ⊕○○○○<br>MUY BAJA | CRÍTICO     |
| Duración de la estancia hospitalaria (agudización actual) |                          |                    |                    |                     |                    |                       |                          |                           |                        |                                              |                   |             |
| 1                                                         | estudios observacionales | serio <sup>c</sup> | no es serio        | no es serio         | no es serio        | ninguno               | 39                       | 34                        | -                      | MD 0.2 menos (1.73 menos a 1.33 más )        | ⊕○○○○<br>MUY BAJA | IMPORTANTE  |
| Número de nuevas agudizaciones                            |                          |                    |                    |                     |                    |                       |                          |                           |                        |                                              |                   |             |
| 1                                                         | estudios observacionales | serio <sup>c</sup> | no es serio        | no es serio         | serio <sup>d</sup> | ninguno               | 8/39 (20.5%)             | 7/34 (20.6%)              | RR 1.00 (0.40 a 2.46)  | 0 menos por 1000 (de 124 menos a 301 más )   | ⊕○○○○<br>MUY BAJA | IMPORTANTE  |
| Número de nuevas hospitalizaciones                        |                          |                    |                    |                     |                    |                       |                          |                           |                        |                                              |                   |             |
| 1                                                         | estudios observacionales | serio <sup>c</sup> | no es serio        | no es serio         | serio <sup>d</sup> | ninguno               | 4/39 (10.3%)             | 5/34 (14.7%)              | RR 0.70 (0.20 a 2.39)  | 44 menos por 1000 (de 118 menos a 204 más )  | ⊕○○○○<br>MUY BAJA | IMPORTANTE  |
| Identificación de bacterias potencialmente patológicas    |                          |                    |                    |                     |                    |                       |                          |                           |                        |                                              |                   |             |
| 6                                                         | estudios observacionales | serio <sup>e</sup> | serio <sup>b</sup> | serio <sup>f</sup>  | no es serio        | ninguno               | 670/771 (86.9%)          | 164/321 (51.1%)           | RR 2.14 (1.26 a 3.67)  | 582 más por 1000 (de 133 más a 1000 más )    | ⊕○○○○<br>MUY BAJA | IMPORTANTE  |

CI: Intervalo de confianza ; RR: Razón de riesgo; MD: Diferencia media

## Explicaciones

- a. Resultados no ajustados a otros factores de riesgo. Evaluación subjetiva del esputo por parte de los pacientes en un estudio.
- b. Variabilidad significativa en los resultados de los diferentes estudios.
- c. Estudio con evaluación subjetiva del esputo por parte de los pacientes.
- d. Número muy escaso de eventos
- e. Ninguno de los estudios presentó unos resultados ajustados a otros factores de riesgo. Evaluación subjetiva del esputo por parte de los pacientes en dos estudios.
- f. Desenlace subrogado de los desenlaces clínicos relevantes

### PREGUNTA 3

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <p><b>Pregunta para responder:</b><br/> <b>¿La determinación de la proteína C-reactiva (PCR), es útil para guiar la administración de antibióticos en los pacientes con una agudización de la EPOC?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                |
| <p>Se identificaron tres referencias relevantes, que incluían el mismo ensayo clínico aleatorizado (ECA) que evalúa el impacto sobre el uso de antibióticos y otros desenlaces clínicos de determinación de proteína C reactiva (PCR) en comparación con el tratamiento antibiótico guiado por criterios clínicos habituales.</p> <p>Para el análisis se incluyeron los resultados de tres publicaciones de un solo ensayo aleatorizado y abierto. Este estudio aleatorizó a 653 pacientes, de 40 años o más, con un diagnóstico de EPOC en atención primaria y una agudización definida como incremento de la disnea o aumento de la producción o purulencia del esputo de 24 horas y 21 días de duración. Se excluyeron los pacientes que requirieron ingreso hospitalario.</p> <p>El grupo asignado a tratamiento antibiótico guiado por la determinación de PCR se rigió según los siguientes criterios:<br/> Niveles de PCR &lt; 20 mg/l: el tratamiento antibiótico es poco probable que sea beneficioso y no se debería prescribir.<br/> Niveles de PCR entre 20 y 40 mg/l: el tratamiento antibiótico puede ser beneficioso si el paciente presenta esputo purulento.<br/> Niveles de PCR &gt; 40 mg/l: el tratamiento antibiótico probablemente sea beneficioso.</p> <p><b>Ensayos clínicos aleatorizados:</b></p> <ol style="list-style-type: none"> <li>1. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, et al. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. N Engl J Med. 2019;381(2):111-20.</li> <li>2. Francis NA, Gillespie D, White P, Bates J, Lowe R, Sewell B, et al. C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT. Health Technol Assess. 2020;24(15):1-108.</li> <li>3. Phillips R, Stanton H, Singh-Mehta A, Gillespie D, Bates J, Gal M, et al. C-reactive protein-guided antibiotic prescribing for COPD exacerbations: a qualitative evaluation. Br J Gen Pract. 2020.</li> </ol> |                                |
| <p><b>Consumo de antibióticos</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                |
| <p>El tratamiento con antibióticos guiado por PCR muestra una reducción del consumo de antibióticos (durante las 4 semanas posteriores) respecto un tratamiento guiado por criterios habituales: OR 0.31 (0.20 a 0.47); 259 menos por 1000 (de 368 menos a 157 menos).</p> <p>Los resultados crudos muestran que un 57% de los pacientes del grupo guiado por CRP consumieron antibióticos frente a un 77,4% del grupo guiado por criterios habituales.</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p><b>Calidad moderada</b></p> |
| <p><b>Estado de salud (cuestionario clínico sobre la EPOC, CCQ)</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                |
| <p>El tratamiento con antibióticos guiado por PCR muestra una reducción del estado de salud medido con el cuestionario CCQ respecto un tratamiento guiado por criterios habituales: MD 0.19 puntos menos (0.33 a 0.05 menos).</p> <p>Según el extremo inferior del intervalo de confianza (-0,33 puntos) no se puede concluir la no inferioridad, es decir que la reducción de la prescripción de antibióticos guiada por PCR conlleve a una reducción clínicamente significativa del estado de salud</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p><b>Calidad baja</b></p>     |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|
| La confianza con los resultados es baja (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                         |                         |
| <b>Prescripción de antibióticos</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                         |                         |
| <p>El tratamiento con antibióticos guiado por PCR muestra una reducción del tratamiento con antibióticos (en el momento de la consulta médica) respecto un tratamiento guiado por criterios habituales: OR 0.31 (0.21 a 0.45); 256 menos por 1000 (de 357 menos a 153 menos).</p> <p>Los resultados crudos muestran que un 47,7% de los pacientes del grupo guiado por PCR recibieron antibióticos en el momento de la consulta frente a un 69,7% del grupo guiado por criterios habituales.</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                               | <b>Calidad moderada</b> |                         |
| <b>Calidad de vida (EQ-5D)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                         |                         |
| <p>En el ECA seleccionado se reporta datos (1874 respuestas de 548 pacientes) sobre la calidad de vida hasta los 6 meses posteriores de los pacientes con agudizaciones de la EPOC.</p> <p>El tratamiento con antibióticos guiado por PCR muestra una mejor calidad de vida respecto a un tratamiento guiado por criterios habituales: MD 3.12 más (0.5 a 5.74 más).</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                                                                                                                                                       |                         | <b>Calidad moderada</b> |
| <b>Hospitalización</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                         |                         |
| <p>Durante 6 meses de seguimiento, 26 de los 304 pacientes (8.6%) en el grupo guiado por PCR tuvieron 35 hospitalizaciones, y 28 de 301 pacientes (9.3%) en el grupo de tratamiento guiado por criterios habituales tuvieron 34 hospitalizaciones.</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados)</p>                                                                                                                                                                                                                                                                              | <b>Calidad baja</b>     |                         |
| <b>Eventos adversos</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                         |                         |
| <p>Los resultados no muestran diferencias significativas entre el tratamiento con antibióticos guiado por PCR y el placebo: OR 0.79 (0.44 a 1.39); 21 menos a 23 más).</p> <p>Durante las primeras 4 semanas de seguimiento, se informaron dos eventos adversos graves (uno por neumonía y otro por insuficiencia respiratoria) en el grupo placebo. Ambos fueron eventos en los que los pacientes fallecieron. Ambos eventos no se consideraron que estuvieran relacionados con la intervención o participación en el estudio.</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados)</p> |                         | <b>Calidad baja</b>     |
| <b>Balance entre beneficios y riesgos</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                         |                         |
| <p>El tratamiento de antibióticos guiado por PCR se asocia a una reducción en el consumo de antibióticos y a mejor calidad de vida relacionada con la salud, sin efectos adversos relevantes, aunque con un mayor coste para el sistema nacional de salud.</p>                                                                                                                                                                                                                                                                                                                                                          |                         |                         |
| <b>Calidad global de la evidencia</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                         |                         |
| <p>Ninguno de los desenlaces evaluados en los estudios se consideró clave según el grupo de autores. La confianza con los desenlaces importantes fue entre baja y moderada debido al diseño de los estudios y a la imprecisión de los resultados.</p>                                                                                                                                                                                                                                                                                                                                                                   |                         |                         |
| <b>Uso de recursos y costes</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                         |
| <p>El ECA incluido presentó también resultados de un estudio económico en una publicación independiente (Francis 2020).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                         |                         |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>A las cuatro semanas de seguimiento, los pacientes del grupo guiado por PCR tienen un mayor coste al sistema nacional de salud respecto a los pacientes del grupo guiado por criterios habituales: £17.59 más por paciente (95% IC: £-17.59 a £69.98; <math>P = 0.408</math>). La media del índice de costo-efectividad incremental fue de £222 por 1% reducción en el consumo de antibióticos en comparación con el tratamiento habitual. A los 6 meses de seguimiento, la media del índice de costo-efectividad incremental fue de £15.251 por año de vida ajustado por calidad.</p> |
| <p><b>Recomendaciones</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p>Se sugiere guiar el tratamiento antibiótico con la determinación de proteína C-reactiva (PCR) en los pacientes con una agudización de la EPOC en los que la valoración del cambio en el color del esputo no sea concluyente (recomendación débil, calidad de evidencia baja)</p>                                                                                                                                                                                                                                                                                                       |
| <p><b>Especificaciones</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p>En pacientes con PCR elevada (<math>\geq 20</math> mg/l) estará indicado el tratamiento con antibióticos.</p> <p>Este biomarcador puede ser empleado tanto en medio hospitalario, como ambulatorio (PCR capilar).</p>                                                                                                                                                                                                                                                                                                                                                                  |

Pregunta: ¿La determinación de la proteína C-reactiva (PCR), es útil para guiar la administración de antibióticos en los pacientes con una agudización de la EPOC?

| Certainty assessment                                                                                                |                    |                    |                |                     |                    |                       | Nº de pacientes                 |                 | Efecto                |                                                 | Certainty        | Importancia |
|---------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|----------------|---------------------|--------------------|-----------------------|---------------------------------|-----------------|-----------------------|-------------------------------------------------|------------------|-------------|
| Nº de estudios                                                                                                      | Diseño de estudio  | Riesgo de sesgo    | Inconsistencia | Evidencia indirecta | Imprecisión        | Otras consideraciones | CRP-guided antibiotic treatment | placebo         | Relativo (95% CI)     | Absoluto (95% CI)                               |                  |             |
| Consumo antibióticos                                                                                                |                    |                    |                |                     |                    |                       |                                 |                 |                       |                                                 |                  |             |
| 1                                                                                                                   | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | no es serio        | ninguno               | 150/263 (57.0%)                 | 212/274 (77.4%) | OR 0.31 (0.20 a 0.47) | 259 menos por 1000 (de 368 menos a 157 menos )  | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Estado de salud (cuestionario clínico sobre la EPOC) (seguimiento: 2 semanas; evaluado con : CCQ; Escala de: 0 a 6) |                    |                    |                |                     |                    |                       |                                 |                 |                       |                                                 |                  |             |
| 1                                                                                                                   | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | serio <sup>b</sup> | ninguno               | 281                             | 282             | -                     | MD 0.19 puntos menos (0.33 menos a 0.05 menos ) | ⊕⊕○○<br>BAJA     | IMPORTANTE  |
| Prescripción de antibióticos (seguimiento: 4 semanas)                                                               |                    |                    |                |                     |                    |                       |                                 |                 |                       |                                                 |                  |             |
| 1                                                                                                                   | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | no es serio        | ninguno               | 185/313 (59.1%)                 | 252/316 (79.7%) | OR 0.30 (0.20 a 0.46) | 256 menos por 1000 (de 357 menos a 153 menos )  | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Calidad de vida (seguimiento: 6 meses ; evaluado con : EQ-5D)                                                       |                    |                    |                |                     |                    |                       |                                 |                 |                       |                                                 |                  |             |
| 1                                                                                                                   | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | no es serio        | ninguno               | 281                             | 282             | -                     | MD 3.12 más (0.5 más a 5.74 más )               | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Eventos adversos (seguimiento: 4 semanas)                                                                           |                    |                    |                |                     |                    |                       |                                 |                 |                       |                                                 |                  |             |
| 1                                                                                                                   | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | serio <sup>c</sup> | ninguno               | 255/285 (89.5%)                 | 264/289 (91.3%) | OR 0.79 (0.44 a 1.39) | 21 menos por 1000 (de 91 menos a 23 más )       | ⊕⊕○○<br>BAJA     | IMPORTANTE  |

CI: Intervalo de confianza ; OR: Razón de momios; MD: Diferencia media

Explicaciones

a. Estudio abierto, no se excluye la posibilidad de sesgo debido a la evaluación de desenlaces de naturaleza subjetiva  
b. El extremo inferior del IC95% no excluye un efecto negativo clínicamente relevante (en la publicación del estudio no se excluyó la no-inferioridad).  
c. IC95% muy amplio que incluye un efeto relevante tanto beneficioso como perjudicial



#### PREGUNTA 4

##### **Pregunta para responder:**

**¿La determinación de la procalcitonina (PCT), es útil para guiar la administración de antibióticos en los pacientes con una agudización de la EPOC?**

Se identificaron cuatro revisiones sistemáticas, que incluían 11 ensayos clínicos aleatorizados (ECAs) que evaluaron la efectividad del tratamiento con antibióticos guiado por procalcitonina (PCT) en comparación con el tratamiento guiado por criterios clínicos habituales. Posteriormente no se ha identificado ningún estudio adicional relevante.

Todos los estudios incluyeron pacientes hospitalizados; uno de ellos (Daubin 2018) incluyó pacientes ingresados en una UCI por insuficiencia respiratoria aguda debido a una agudización de la EPOC.

##### **Revisiones sistemáticas:**

1. Li Z, Yuan X, Yu L, Wang B, Gao F, Ma J. Procalcitonin-guided antibiotic therapy in acute exacerbation of chronic obstructive pulmonary disease: An updated meta-analysis. *Medicine (Baltimore)*. 2019;98(32):e16775.
2. Ni W, Bao J, Yang D, Xi W, Wang K, Xu Y, et al. Potential of serum procalcitonin in predicting bacterial exacerbation and guiding antibiotic administration in severe COPD exacerbations: a systematic review and meta-analysis. *Infect Dis (Lond)*. 2019;51(9):639-50.
3. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Vestbo J. Procalcitonin to guide antibiotic administration in COPD exacerbations: A meta-analysis. *European Respiratory Review*. 2017;26(143).
4. Lin C, Pang Q. Meta-analysis and systematic review of procalcitonin-guided treatment in acute exacerbation of chronic obstructive pulmonary disease. *Clinical Respiratory Journal*. 2018;12(1):10-5.

##### **Ensayos clínicos aleatorizados:**

1. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet*. 2004; 363:600–607.
2. Corti C, Fally M, Fabricius-Bjerre A, et al. Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* 2016; 11:1381–1389.
3. Daubin C, Valette X, Thiollere F, et al. Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study. *Intensive Care Med*. 2018; 44:428–437.
4. Huang DT, Yealy DM, Filbin MR, et al. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. *N Engl J Med*. 2018; 379:236–249.
5. Kristoffersen KB, Sogaard OS, Wejse C, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission – a randomized trial. *Clin Microbiol Infect* 2009; 15: 481–487.
6. Liu SS, Zhang YB. The value of serum procalcitonin level in guiding the use of antibiotic in patients with acute exacerbation of chronic obstructive pulmonary disease. *Chin J Antibiot*. 2015; 40:459–463.
7. Nangia V, Gandhi K. Use of procalcitonin to guide the antibiotic therapy in patients with an acute exacerbation of COPD in a resource-limited setting: a case-control study. *Clin Microbiol Infect*. 2012; 18:O404.
8. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin- based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA*. 2009; 302:1059–1066.
9. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007; 131:9–19.
10. Verduri A, Luppi F, D'Amico R, et al. Antibiotic treatment of severe exacerbations of chronic obstructive pulmonary disease with procalcitonin: a randomized noninferiority trial. *PloS One*. 2015;10:e0118241.

11. Wang JX, Zhang SM, Li XH, et al. Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial. *Int J Infect Dis.* 2016;48:40–45.

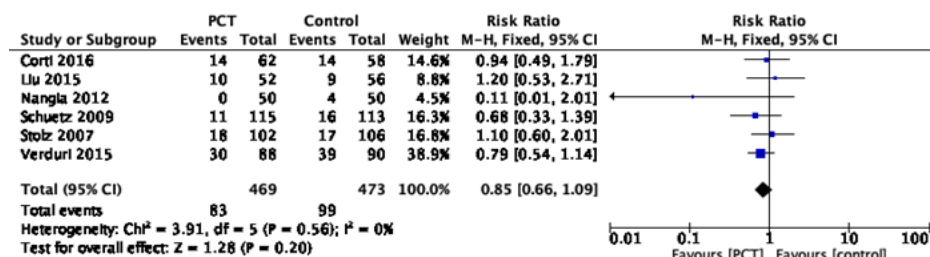
### Tratamiento con antibióticos guiado por procalcitonina vs tratamiento con criterios clínicos habituales (placebo)

#### Fracaso terapéutico

En el análisis conjunto de los datos (6 ECAs, 182 eventos), el tratamiento con antibióticos guiado por procalcitonina no muestra una diferencia significativa respecto a placebo: RR 0.85 (0.66 a 1.09); 31 menos por 1000 (de 71 menos a 19 más).

La confianza con los resultados es baja (ver tabla de resumen de resultados).

**Calidad baja**

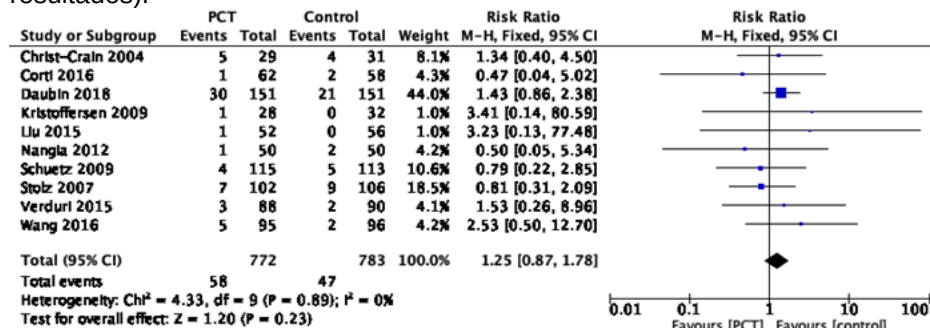


#### Mortalidad por cualquier causa

En el análisis conjunto de los datos (10 ECAs, 105 eventos), no se observa una diferencia significativa en la mortalidad por cualquier causa entre el tratamiento con antibióticos guiado por procalcitonina y el placebo: RR 1.25 (0.87 a 1.78); 15 más por 1000 (de 8 menos a 47 más).

La confianza con los resultados es moderada (ver tabla de resumen de resultados).

**Calidad moderada**



#### Duración estancia hospitalaria

En el análisis conjunto de los datos (11 ECAs, 2108 pacientes), no se observa una diferencia significativa en la estancia hospitalaria entre el tratamiento con antibióticos guiado por procalcitonina y el placebo: 0.03 días menos (-1.03 menos a 0.97 más).

La confianza con los resultados es moderada (ver tabla de resumen de resultados).

**Calidad moderada**

| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">PCT</th><th colspan="3">Control</th><th rowspan="2">Weight</th><th rowspan="2">Mean Difference<br/>IV, Random, 95% CI</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Christ-Crain 2004</td><td>13.7</td><td>7.3</td><td>29</td><td>10.8</td><td>7</td><td>31</td><td>5.5%</td><td>2.90 [-0.72, 6.52]</td></tr><tr><td>Corti 2016</td><td>4.5</td><td>2.96</td><td>62</td><td>5.1</td><td>4.44</td><td>58</td><td>12.9%</td><td>-0.60 [-1.96, 0.76]</td></tr><tr><td>Daubin 2018</td><td>18.85</td><td>18.29</td><td>151</td><td>14.82</td><td>9.48</td><td>151</td><td>6.2%</td><td>4.03 [0.74, 7.32]</td></tr><tr><td>Huang 2018</td><td>5.4</td><td>4.8</td><td>265</td><td>4.6</td><td>3.1</td><td>259</td><td>15.5%</td><td>0.80 [0.11, 1.49]</td></tr><tr><td>Kristoffersen 2009</td><td>4.8</td><td>2.8368</td><td>38</td><td>7.1</td><td>3.6057</td><td>51</td><td>13.0%</td><td>-2.30 [-3.64, -0.96]</td></tr><tr><td>Liu 2015</td><td>16.06</td><td>4.73</td><td>52</td><td>19.41</td><td>6.74</td><td>56</td><td>9.6%</td><td>-3.35 [-5.53, -1.17]</td></tr><tr><td>Nangia 2012</td><td>7.5</td><td>2.5</td><td>50</td><td>7.3</td><td>2.3</td><td>50</td><td>14.6%</td><td>0.20 [-0.74, 1.14]</td></tr><tr><td>Schuetz 2009</td><td>8.8</td><td>51.23</td><td>115</td><td>9.2</td><td>51.23</td><td>113</td><td>0.6%</td><td>-0.40 [-13.70, 12.90]</td></tr><tr><td>Stolz 2007</td><td>9</td><td>30.547</td><td>102</td><td>10</td><td>25.9622</td><td>106</td><td>1.6%</td><td>-1.00 [-8.72, 6.72]</td></tr><tr><td>Verduri 2015</td><td>5</td><td>7.0795</td><td>88</td><td>5</td><td>7.1618</td><td>90</td><td>9.9%</td><td>0.00 [-2.09, 2.09]</td></tr><tr><td>Wang 2016</td><td>10.9</td><td>8.1</td><td>95</td><td>9.9</td><td>5.1</td><td>96</td><td>10.6%</td><td>1.00 [-0.92, 2.92]</td></tr><tr><td>Total (95% CI)</td><td></td><td></td><td>1047</td><td></td><td></td><td>1061</td><td>100.0%</td><td>-0.05 [-1.08, 0.99]</td></tr></table> <p>Heterogeneity: <math>\tau^2 = 1.67</math>; <math>\chi^2 = 35.66</math>, <math>df = 10</math> (<math>P &lt; 0.0001</math>); <math>I^2 = 72\%</math><br/>Test for overall effect: <math>Z = 0.09</math> (<math>P = 0.93</math>)</p> | Study or Subgroup              | PCT    |        |         | Control |                   |                                   | Weight                | Mean Difference<br>IV, Random, 95% CI | Mean   | SD                                    | Total             | Mean | SD | Total | Christ-Crain 2004 | 13.7 | 7.3               | 29         | 10.8 | 7   | 31 | 5.5%  | 2.90 [-0.72, 6.52]   | Corti 2016        | 4.5         | 2.96 | 62  | 5.1 | 4.44 | 58    | 12.9%             | -0.60 [-1.96, 0.76]  | Daubin 2018 | 18.85 | 18.29 | 151 | 14.82 | 9.48              | 151                | 6.2%  | 4.03 [0.74, 7.32]  | Huang 2018 | 5.4 | 4.8   | 265               | 4.6      | 3.1 | 259 | 15.5% | 0.80 [0.11, 1.49]  | Kristoffersen 2009 | 4.8           | 2.8368      | 38 | 7.1   | 3.6057 | 51 | 13.0% | -2.30 [-3.64, -0.96] | Liu 2015     | 16.06 | 4.73 | 52 | 19.41 | 6.74  | 56                | 9.6%       | -3.35 [-5.53, -1.17] | Nangia 2012  | 7.5 | 2.5    | 50    | 7.3               | 2.3          | 50  | 14.6% | 0.20 [-0.74, 1.14]   | Schuetz 2009 | 8.8   | 51.23             | 115       | 9.2 | 51.23 | 113 | 0.6%  | -0.40 [-13.70, 12.90] | Stolz 2007        | 9              | 30.547 | 102  | 10 | 25.9622 | 106    | 1.6%              | -1.00 [-8.72, 6.72]  | Verduri 2015 | 5 | 7.0795 | 88 | 5 | 7.1618 | 90 | 9.9% | 0.00 [-2.09, 2.09] | Wang 2016 | 10.9 | 8.1 | 95 | 9.9 | 5.1 | 96 | 10.6% | 1.00 [-0.92, 2.92] | Total (95% CI) |  |  | 1047 |  |  | 1061 | 100.0% | -0.05 [-1.08, 0.99] |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------|--------|---------|---------|-------------------|-----------------------------------|-----------------------|---------------------------------------|--------|---------------------------------------|-------------------|------|----|-------|-------------------|------|-------------------|------------|------|-----|----|-------|----------------------|-------------------|-------------|------|-----|-----|------|-------|-------------------|----------------------|-------------|-------|-------|-----|-------|-------------------|--------------------|-------|--------------------|------------|-----|-------|-------------------|----------|-----|-----|-------|--------------------|--------------------|---------------|-------------|----|-------|--------|----|-------|----------------------|--------------|-------|------|----|-------|-------|-------------------|------------|----------------------|--------------|-----|--------|-------|-------------------|--------------|-----|-------|----------------------|--------------|-------|-------------------|-----------|-----|-------|-----|-------|-----------------------|-------------------|----------------|--------|------|----|---------|--------|-------------------|----------------------|--------------|---|--------|----|---|--------|----|------|--------------------|-----------|------|-----|----|-----|-----|----|-------|--------------------|----------------|--|--|------|--|--|------|--------|---------------------|--|
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                | PCT    |        |         | Control |                   |                                   |                       |                                       | Weight | Mean Difference<br>IV, Random, 95% CI |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Mean                           | SD     | Total  | Mean    | SD      | Total             |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Christ-Crain 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 13.7                           | 7.3    | 29     | 10.8    | 7       | 31                | 5.5%                              | 2.90 [-0.72, 6.52]    |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Corti 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 4.5                            | 2.96   | 62     | 5.1     | 4.44    | 58                | 12.9%                             | -0.60 [-1.96, 0.76]   |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Daubin 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 18.85                          | 18.29  | 151    | 14.82   | 9.48    | 151               | 6.2%                              | 4.03 [0.74, 7.32]     |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Huang 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 5.4                            | 4.8    | 265    | 4.6     | 3.1     | 259               | 15.5%                             | 0.80 [0.11, 1.49]     |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Kristoffersen 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 4.8                            | 2.8368 | 38     | 7.1     | 3.6057  | 51                | 13.0%                             | -2.30 [-3.64, -0.96]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Liu 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 16.06                          | 4.73   | 52     | 19.41   | 6.74    | 56                | 9.6%                              | -3.35 [-5.53, -1.17]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Nangia 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 7.5                            | 2.5    | 50     | 7.3     | 2.3     | 50                | 14.6%                             | 0.20 [-0.74, 1.14]    |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Schuetz 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 8.8                            | 51.23  | 115    | 9.2     | 51.23   | 113               | 0.6%                              | -0.40 [-13.70, 12.90] |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Stolz 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 9                              | 30.547 | 102    | 10      | 25.9622 | 106               | 1.6%                              | -1.00 [-8.72, 6.72]   |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Verduri 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 5                              | 7.0795 | 88     | 5       | 7.1618  | 90                | 9.9%                              | 0.00 [-2.09, 2.09]    |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Wang 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 10.9                           | 8.1    | 95     | 9.9     | 5.1     | 96                | 10.6%                             | 1.00 [-0.92, 2.92]    |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                |        | 1047   |         |         | 1061              | 100.0%                            | -0.05 [-1.08, 0.99]   |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| <p><b>Prescripción de antibióticos</b></p> <p>En el análisis conjunto de los datos (11 ECA, 2099 pacientes), el tratamiento con antibióticos guiado por procalcitonina muestra una reducción significativa de la prescripción de antibióticos respecto a placebo: RR 0.55 (0.42 a 0.72); 304 menos por 1000 (de 391 menos a 189 menos).</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <p><b>Calidad moderada</b></p> |        |        |         |         |                   |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">PCT</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th rowspan="2">Risk Ratio<br/>M-H, Random, 95% CI</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th></tr><tr><td>Christ-Crain 2004</td><td>11</td><td>29</td><td>27</td><td>31</td><td>8.5%</td><td>0.44 [0.27, 0.71]</td></tr><tr><td>Corti 2016</td><td>36</td><td>62</td><td>43</td><td>58</td><td>10.4%</td><td>0.78 [0.60, 1.02]</td></tr><tr><td>Daubin 2018</td><td>89</td><td>151</td><td>93</td><td>151</td><td>11.0%</td><td>0.96 [0.80, 1.15]</td></tr><tr><td>Huang 2018</td><td>108</td><td>265</td><td>115</td><td>259</td><td>10.9%</td><td>0.92 [0.75, 1.12]</td></tr><tr><td>Kristoffersen 2009</td><td>26</td><td>38</td><td>41</td><td>42</td><td>10.7%</td><td>0.70 [0.56, 0.87]</td></tr><tr><td>Liu 2015</td><td>0</td><td>52</td><td>0</td><td>56</td><td></td><td>Not estimable</td></tr><tr><td>Nangia 2012</td><td>9</td><td>50</td><td>50</td><td>50</td><td>7.6%</td><td>0.19 [0.11, 0.33]</td></tr><tr><td>Schuetz 2009</td><td>56</td><td>115</td><td>79</td><td>113</td><td>10.7%</td><td>0.70 [0.56, 0.87]</td></tr><tr><td>Stolz 2007</td><td>41</td><td>102</td><td>76</td><td>106</td><td>10.4%</td><td>0.56 [0.43, 0.73]</td></tr><tr><td>Verduri 2015</td><td>43</td><td>88</td><td>90</td><td>90</td><td>10.8%</td><td>0.49 [0.40, 0.61]</td></tr><tr><td>Wang 2016</td><td>17</td><td>96</td><td>95</td><td>95</td><td>9.0%</td><td>0.18 [0.12, 0.28]</td></tr><tr><td>Total (95% CI)</td><td></td><td>1048</td><td></td><td>1051</td><td>100.0%</td><td>0.55 [0.42, 0.72]</td></tr></table> <p>Total events: 436 (PCT), 709 (Control)<br/>Heterogeneity: <math>\tau^2 = 0.17</math>; <math>\chi^2 = 98.23</math>, <math>df = 9</math> (<math>P &lt; 0.00001</math>); <math>I^2 = 91\%</math><br/>Test for overall effect: <math>Z = 4.35</math> (<math>P &lt; 0.0001</math>)</p>                                                                                                                                                                                                                                                                                                                                                  | Study or Subgroup              | PCT    |        | Control |         | Weight            | Risk Ratio<br>M-H, Random, 95% CI | Events                | Total                                 | Events | Total                                 | Christ-Crain 2004 | 11   | 29 | 27    | 31                | 8.5% | 0.44 [0.27, 0.71] | Corti 2016 | 36   | 62  | 43 | 58    | 10.4%                | 0.78 [0.60, 1.02] | Daubin 2018 | 89   | 151 | 93  | 151  | 11.0% | 0.96 [0.80, 1.15] | Huang 2018           | 108         | 265   | 115   | 259 | 10.9% | 0.92 [0.75, 1.12] | Kristoffersen 2009 | 26    | 38                 | 41         | 42  | 10.7% | 0.70 [0.56, 0.87] | Liu 2015 | 0   | 52  | 0     | 56                 |                    | Not estimable | Nangia 2012 | 9  | 50    | 50     | 50 | 7.6%  | 0.19 [0.11, 0.33]    | Schuetz 2009 | 56    | 115  | 79 | 113   | 10.7% | 0.70 [0.56, 0.87] | Stolz 2007 | 41                   | 102          | 76  | 106    | 10.4% | 0.56 [0.43, 0.73] | Verduri 2015 | 43  | 88    | 90                   | 90           | 10.8% | 0.49 [0.40, 0.61] | Wang 2016 | 17  | 96    | 95  | 95    | 9.0%                  | 0.18 [0.12, 0.28] | Total (95% CI) |        | 1048 |    | 1051    | 100.0% | 0.55 [0.42, 0.72] |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                | PCT    |        | Control |         |                   |                                   | Weight                | Risk Ratio<br>M-H, Random, 95% CI     |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Events                         | Total  | Events | Total   |         |                   |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Christ-Crain 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 11                             | 29     | 27     | 31      | 8.5%    | 0.44 [0.27, 0.71] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Corti 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 36                             | 62     | 43     | 58      | 10.4%   | 0.78 [0.60, 1.02] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Daubin 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 89                             | 151    | 93     | 151     | 11.0%   | 0.96 [0.80, 1.15] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Huang 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 108                            | 265    | 115    | 259     | 10.9%   | 0.92 [0.75, 1.12] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Kristoffersen 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 26                             | 38     | 41     | 42      | 10.7%   | 0.70 [0.56, 0.87] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Liu 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0                              | 52     | 0      | 56      |         | Not estimable     |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Nangia 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 9                              | 50     | 50     | 50      | 7.6%    | 0.19 [0.11, 0.33] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Schuetz 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 56                             | 115    | 79     | 113     | 10.7%   | 0.70 [0.56, 0.87] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Stolz 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 41                             | 102    | 76     | 106     | 10.4%   | 0.56 [0.43, 0.73] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Verduri 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 43                             | 88     | 90     | 90      | 10.8%   | 0.49 [0.40, 0.61] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Wang 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 17                             | 96     | 95     | 95      | 9.0%    | 0.18 [0.12, 0.28] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                | 1048   |        | 1051    | 100.0%  | 0.55 [0.42, 0.72] |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| <p><b>Duración del tratamiento antibiótico</b></p> <p>En el análisis conjunto de los datos (8 ECAs, 1602), el tratamiento con antibióticos guiado por procalcitonina muestra una reducción en la duración del tratamiento con antibióticos respecto a placebo: MD 2.54 días menos (4.27 a 0.81 menos).</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p><b>Calidad moderada</b></p> |        |        |         |         |                   |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">PCT</th><th colspan="3">Control</th><th rowspan="2">Weight</th><th rowspan="2">Mean Difference<br/>IV, Random, 95% CI</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Christ-Crain 2004</td><td>3.3</td><td>2.1</td><td>29</td><td>7.92</td><td>2.8</td><td>31</td><td>12.9%</td><td>-4.62 [-5.87, -3.37]</td></tr><tr><td>Corti 2016</td><td>6.1</td><td>7.41</td><td>62</td><td>9</td><td>7.4</td><td>58</td><td>10.4%</td><td>-2.90 [-5.55, -0.25]</td></tr><tr><td>Daubin 2018</td><td>7.9</td><td>8</td><td>151</td><td>7.7</td><td>5.7</td><td>151</td><td>12.4%</td><td>0.20 [-1.37, 1.77]</td></tr><tr><td>Huang 2018</td><td>3</td><td>3.9</td><td>265</td><td>2.8</td><td>2.4</td><td>259</td><td>13.6%</td><td>0.20 [-0.35, 0.75]</td></tr><tr><td>Kristoffersen 2009</td><td>4.368</td><td>4.2228</td><td>38</td><td>6.461</td><td>6.2536</td><td>52</td><td>11.4%</td><td>-2.09 [-4.26, 0.07]</td></tr><tr><td>Nangia 2012</td><td>2.1</td><td>2.62</td><td>50</td><td>7.02</td><td>2.6</td><td>50</td><td>13.2%</td><td>-4.92 [-5.94, -3.90]</td></tr><tr><td>Schuetz 2009</td><td>2.5</td><td>5.6622</td><td>115</td><td>5.1</td><td>5.6622</td><td>113</td><td>12.6%</td><td>-2.60 [-4.07, -1.13]</td></tr><tr><td>Verduri 2015</td><td>6.42</td><td>3.519</td><td>88</td><td>10</td><td>0.1</td><td>90</td><td>13.5%</td><td>-3.58 [-4.32, -2.84]</td></tr><tr><td>Total (95% CI)</td><td></td><td></td><td>798</td><td></td><td></td><td>804</td><td>100.0%</td><td>-2.54 [-4.27, -0.81]</td></tr></table> <p>Heterogeneity: <math>\tau^2 = 5.62</math>; <math>\chi^2 = 135.37</math>, <math>df = 7</math> (<math>P &lt; 0.00001</math>); <math>I^2 = 95\%</math><br/>Test for overall effect: <math>Z = 2.88</math> (<math>P = 0.004</math>)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                      | Study or Subgroup              | PCT    |        |         | Control |                   |                                   | Weight                | Mean Difference<br>IV, Random, 95% CI | Mean   | SD                                    | Total             | Mean | SD | Total | Christ-Crain 2004 | 3.3  | 2.1               | 29         | 7.92 | 2.8 | 31 | 12.9% | -4.62 [-5.87, -3.37] | Corti 2016        | 6.1         | 7.41 | 62  | 9   | 7.4  | 58    | 10.4%             | -2.90 [-5.55, -0.25] | Daubin 2018 | 7.9   | 8     | 151 | 7.7   | 5.7               | 151                | 12.4% | 0.20 [-1.37, 1.77] | Huang 2018 | 3   | 3.9   | 265               | 2.8      | 2.4 | 259 | 13.6% | 0.20 [-0.35, 0.75] | Kristoffersen 2009 | 4.368         | 4.2228      | 38 | 6.461 | 6.2536 | 52 | 11.4% | -2.09 [-4.26, 0.07]  | Nangia 2012  | 2.1   | 2.62 | 50 | 7.02  | 2.6   | 50                | 13.2%      | -4.92 [-5.94, -3.90] | Schuetz 2009 | 2.5 | 5.6622 | 115   | 5.1               | 5.6622       | 113 | 12.6% | -2.60 [-4.07, -1.13] | Verduri 2015 | 6.42  | 3.519             | 88        | 10  | 0.1   | 90  | 13.5% | -3.58 [-4.32, -2.84]  | Total (95% CI)    |                |        | 798  |    |         | 804    | 100.0%            | -2.54 [-4.27, -0.81] |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                | PCT    |        |         | Control |                   |                                   |                       |                                       | Weight | Mean Difference<br>IV, Random, 95% CI |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Mean                           | SD     | Total  | Mean    | SD      | Total             |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Christ-Crain 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 3.3                            | 2.1    | 29     | 7.92    | 2.8     | 31                | 12.9%                             | -4.62 [-5.87, -3.37]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Corti 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 6.1                            | 7.41   | 62     | 9       | 7.4     | 58                | 10.4%                             | -2.90 [-5.55, -0.25]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Daubin 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 7.9                            | 8      | 151    | 7.7     | 5.7     | 151               | 12.4%                             | 0.20 [-1.37, 1.77]    |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Huang 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 3                              | 3.9    | 265    | 2.8     | 2.4     | 259               | 13.6%                             | 0.20 [-0.35, 0.75]    |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Kristoffersen 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 4.368                          | 4.2228 | 38     | 6.461   | 6.2536  | 52                | 11.4%                             | -2.09 [-4.26, 0.07]   |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Nangia 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 2.1                            | 2.62   | 50     | 7.02    | 2.6     | 50                | 13.2%                             | -4.92 [-5.94, -3.90]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Schuetz 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 2.5                            | 5.6622 | 115    | 5.1     | 5.6622  | 113               | 12.6%                             | -2.60 [-4.07, -1.13]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Verduri 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 6.42                           | 3.519  | 88     | 10      | 0.1     | 90                | 13.5%                             | -3.58 [-4.32, -2.84]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                |        | 798    |         |         | 804               | 100.0%                            | -2.54 [-4.27, -0.81]  |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |
| <p><b>Recurrencia de agudizaciones</b></p> <p>En el análisis conjunto de los datos (7 ECAs, 417 eventos), no se observa una diferencia significativa entre el tratamiento con antibióticos guiado por procalcitonina y el placebo: RR 1.02 (0.91 a 1.15); 8 más por 1000 (de 34 menos a 57 más).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p><b>Calidad baja</b></p>     |        |        |         |         |                   |                                   |                       |                                       |        |                                       |                   |      |    |       |                   |      |                   |            |      |     |    |       |                      |                   |             |      |     |     |      |       |                   |                      |             |       |       |     |       |                   |                    |       |                    |            |     |       |                   |          |     |     |       |                    |                    |               |             |    |       |        |    |       |                      |              |       |      |    |       |       |                   |            |                      |              |     |        |       |                   |              |     |       |                      |              |       |                   |           |     |       |     |       |                       |                   |                |        |      |    |         |        |                   |                      |              |   |        |    |   |        |    |      |                    |           |      |     |    |     |     |    |       |                    |                |  |  |      |  |  |      |        |                     |  |

| <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">PCT</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Fixed, 95% CI</th><th>M-H, Fixed, 95% CI</th></tr></thead><tbody><tr><td>Christ-Crain 2004</td><td>22</td><td>29</td><td>18</td><td>31</td><td>8.4%</td><td>1.31 [0.91, 1.88]</td><td rowspan="7"></td></tr><tr><td>Corti 2016</td><td>60</td><td>62</td><td>56</td><td>58</td><td>28.0%</td><td>1.00 [0.94, 1.07]</td></tr><tr><td>Liu 2015</td><td>14</td><td>44</td><td>15</td><td>46</td><td>7.1%</td><td>0.98 [0.54, 1.78]</td></tr><tr><td>Schuetz 2009</td><td>6</td><td>115</td><td>11</td><td>113</td><td>5.4%</td><td>0.54 [0.21, 1.40]</td></tr><tr><td>Stolz 2007</td><td>63</td><td>102</td><td>71</td><td>106</td><td>33.7%</td><td>0.92 [0.75, 1.13]</td></tr><tr><td>Verduri 2015</td><td>28</td><td>88</td><td>25</td><td>90</td><td>12.0%</td><td>1.15 [0.73, 1.80]</td></tr><tr><td>Wang 2016</td><td>17</td><td>95</td><td>11</td><td>96</td><td>5.3%</td><td>1.56 [0.77, 3.16]</td></tr><tr><td>Total (95% CI)</td><td colspan="2">535</td><td colspan="2">540</td><td>100.0%</td><td>1.02 [0.91, 1.15]</td></tr><tr><td>Total events</td><td colspan="2">210</td><td colspan="2">207</td><td colspan="3"></td></tr><tr><td colspan="8">Heterogeneity: Chi² = 6.43, df = 6 (P = 0.38); I² = 7%</td></tr><tr><td colspan="8">Test for overall effect: Z = 0.34 (P = 0.74)</td></tr></tbody></table> |        |       |         |       |        |                    |                    |  |  | Study or Subgroup   | PCT |  | Control |  | Weight | Risk Ratio |  | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | Christ-Crain 2004 | 22 | 29 | 18 | 31 | 8.4%  | 1.31 [0.91, 1.88] |  | Corti 2016   | 60 | 62 | 56 | 58 | 28.0% | 1.00 [0.94, 1.07] | Liu 2015    | 14 | 44  | 15 | 46  | 7.1%  | 0.98 [0.54, 1.78] | Schuetz 2009   | 6   | 115 | 11  | 113 | 5.4%   | 0.54 [0.21, 1.40] | Stolz 2007   | 63 | 102 | 71 | 106 | 33.7% | 0.92 [0.75, 1.13] | Verduri 2015 | 28                                                     | 88 | 25 | 90 | 12.0% | 1.15 [0.73, 1.80] | Wang 2016      | 17  | 95                                           | 11  | 96 | 5.3%   | 1.56 [0.77, 3.16] | Total (95% CI) | 535 |  | 540 |  | 100.0% | 1.02 [0.91, 1.15] | Total events | 210                                                    |  | 207 |  |  |  |  | Heterogeneity: Chi² = 6.43, df = 6 (P = 0.38); I² = 7% |                                              |  |  |  |  |  |  | Test for overall effect: Z = 0.34 (P = 0.74) |  |  |  |  |  |  |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-------|---------|-------|--------|--------------------|--------------------|--|--|---------------------|-----|--|---------|--|--------|------------|--|--------|-------|--------|-------|--------------------|--------------------|-------------------|----|----|----|----|-------|-------------------|--|--------------|----|----|----|----|-------|-------------------|-------------|----|-----|----|-----|-------|-------------------|----------------|-----|-----|-----|-----|--------|-------------------|--------------|----|-----|----|-----|-------|-------------------|--------------|--------------------------------------------------------|----|----|----|-------|-------------------|----------------|-----|----------------------------------------------|-----|----|--------|-------------------|----------------|-----|--|-----|--|--------|-------------------|--------------|--------------------------------------------------------|--|-----|--|--|--|--|--------------------------------------------------------|----------------------------------------------|--|--|--|--|--|--|----------------------------------------------|--|--|--|--|--|--|--|--|
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | PCT    |       | Control |       | Weight | Risk Ratio         |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Events | Total | Events  | Total |        | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Christ-Crain 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 22     | 29    | 18      | 31    | 8.4%   | 1.31 [0.91, 1.88]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Corti 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 60     | 62    | 56      | 58    | 28.0%  | 1.00 [0.94, 1.07]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Liu 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 14     | 44    | 15      | 46    | 7.1%   | 0.98 [0.54, 1.78]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Schuetz 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 6      | 115   | 11      | 113   | 5.4%   | 0.54 [0.21, 1.40]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Stolz 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 63     | 102   | 71      | 106   | 33.7%  | 0.92 [0.75, 1.13]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Verduri 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 28     | 88    | 25      | 90    | 12.0%  | 1.15 [0.73, 1.80]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Wang 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 17     | 95    | 11      | 96    | 5.3%   | 1.56 [0.77, 3.16]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 535    |       | 540     |       | 100.0% | 1.02 [0.91, 1.15]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 210    |       | 207     |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Heterogeneity: Chi² = 6.43, df = 6 (P = 0.38); I² = 7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 0.34 (P = 0.74)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <b>Reingreso</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| En el análisis conjunto de los datos (6 ECAs, 171 eventos), no se observa una diferencia significativa entre el tratamiento con antibióticos guiado por procalcitonina y el placebo: RR 1.15 (0.88 a 1.50); 25 más por 1000 (de 20 menos a 82 más).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |        |       |         |       |        |                    |                    |  |  | <b>Calidad baja</b> |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| La confianza con los resultados es baja (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">PCT</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Fixed, 95% CI</th><th>M-H, Fixed, 95% CI</th></tr></thead><tbody><tr><td>Christ-Crain 2004</td><td>14</td><td>29</td><td>12</td><td>31</td><td>14.5%</td><td>1.25 [0.70, 2.23]</td><td rowspan="7"></td></tr><tr><td>Corti 2016</td><td>21</td><td>62</td><td>13</td><td>58</td><td>16.8%</td><td>1.51 [0.84, 2.73]</td></tr><tr><td>Daubin 2018</td><td>20</td><td>151</td><td>19</td><td>151</td><td>23.8%</td><td>1.05 [0.59, 1.89]</td></tr><tr><td>Nangla 2012</td><td>0</td><td>50</td><td>1</td><td>50</td><td>1.9%</td><td>0.33 [0.01, 7.99]</td></tr><tr><td>Stolz 2007</td><td>21</td><td>102</td><td>25</td><td>106</td><td>30.7%</td><td>0.87 [0.52, 1.46]</td></tr><tr><td>Verduri 2015</td><td>15</td><td>88</td><td>10</td><td>90</td><td>12.4%</td><td>1.53 [0.73, 3.23]</td></tr><tr><td>Total (95% CI)</td><td colspan="2">482</td><td colspan="2">486</td><td>100.0%</td><td>1.15 [0.88, 1.50]</td></tr><tr><td>Total events</td><td colspan="2">91</td><td colspan="2">80</td><td colspan="3"></td></tr><tr><td colspan="8">Heterogeneity: Chi² = 3.25, df = 5 (P = 0.66); I² = 0%</td></tr><tr><td colspan="8">Test for overall effect: Z = 1.03 (P = 0.30)</td></tr></tbody></table>                                                                                                              |        |       |         |       |        |                    |                    |  |  | Study or Subgroup   | PCT |  | Control |  | Weight | Risk Ratio |  | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | Christ-Crain 2004 | 14 | 29 | 12 | 31 | 14.5% | 1.25 [0.70, 2.23] |  | Corti 2016   | 21 | 62 | 13 | 58 | 16.8% | 1.51 [0.84, 2.73] | Daubin 2018 | 20 | 151 | 19 | 151 | 23.8% | 1.05 [0.59, 1.89] | Nangla 2012    | 0   | 50  | 1   | 50  | 1.9%   | 0.33 [0.01, 7.99] | Stolz 2007   | 21 | 102 | 25 | 106 | 30.7% | 0.87 [0.52, 1.46] | Verduri 2015 | 15                                                     | 88 | 10 | 90 | 12.4% | 1.53 [0.73, 3.23] | Total (95% CI) | 482 |                                              | 486 |    | 100.0% | 1.15 [0.88, 1.50] | Total events   | 91  |  | 80  |  |        |                   |              | Heterogeneity: Chi² = 3.25, df = 5 (P = 0.66); I² = 0% |  |     |  |  |  |  |                                                        | Test for overall effect: Z = 1.03 (P = 0.30) |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | PCT    |       | Control |       | Weight | Risk Ratio         |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Events | Total | Events  | Total |        | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Christ-Crain 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 14     | 29    | 12      | 31    | 14.5%  | 1.25 [0.70, 2.23]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Corti 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 21     | 62    | 13      | 58    | 16.8%  | 1.51 [0.84, 2.73]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Daubin 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 20     | 151   | 19      | 151   | 23.8%  | 1.05 [0.59, 1.89]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Nangla 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0      | 50    | 1       | 50    | 1.9%   | 0.33 [0.01, 7.99]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Stolz 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 21     | 102   | 25      | 106   | 30.7%  | 0.87 [0.52, 1.46]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Verduri 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 15     | 88    | 10      | 90    | 12.4%  | 1.53 [0.73, 3.23]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 482    |       | 486     |       | 100.0% | 1.15 [0.88, 1.50]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 91     |       | 80      |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Heterogeneity: Chi² = 3.25, df = 5 (P = 0.66); I² = 0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 1.03 (P = 0.30)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <b>Reingreso debido a agudización</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| En el análisis conjunto de los datos (3 ECAs, 66 eventos), no se observa una diferencia significativa entre el tratamiento con antibióticos guiado por procalcitonina y el placebo: RR 1.34 (0.85 a 2.10); 39 más por 1000 (de 17 menos a 126 más).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |        |       |         |       |        |                    |                    |  |  | <b>Calidad baja</b> |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| La confianza con los resultados es baja (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <table><thead><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">PCT</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Fixed, 95% CI</th><th>M-H, Fixed, 95% CI</th></tr></thead><tbody><tr><td>Corti 2016</td><td>12</td><td>62</td><td>12</td><td>58</td><td>43.9%</td><td>0.94 [0.46, 1.91]</td><td rowspan="3"></td></tr><tr><td>Verduri 2015</td><td>13</td><td>88</td><td>8</td><td>90</td><td>28.0%</td><td>1.66 [0.72, 3.81]</td></tr><tr><td>Wang 2016</td><td>13</td><td>95</td><td>8</td><td>96</td><td>28.2%</td><td>1.64 [0.71, 3.78]</td></tr><tr><td>Total (95% CI)</td><td colspan="2">245</td><td colspan="2">244</td><td>100.0%</td><td>1.34 [0.85, 2.10]</td></tr><tr><td>Total events</td><td colspan="2">38</td><td colspan="2">28</td><td colspan="3"></td></tr><tr><td colspan="8">Heterogeneity: Chi² = 1.45, df = 2 (P = 0.48); I² = 0%</td></tr><tr><td colspan="8">Test for overall effect: Z = 1.26 (P = 0.21)</td></tr></tbody></table>                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |        |       |         |       |        |                    |                    |  |  | Study or Subgroup   | PCT |  | Control |  | Weight | Risk Ratio |  | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | Corti 2016        | 12 | 62 | 12 | 58 | 43.9% | 0.94 [0.46, 1.91] |  | Verduri 2015 | 13 | 88 | 8  | 90 | 28.0% | 1.66 [0.72, 3.81] | Wang 2016   | 13 | 95  | 8  | 96  | 28.2% | 1.64 [0.71, 3.78] | Total (95% CI) | 245 |     | 244 |     | 100.0% | 1.34 [0.85, 2.10] | Total events | 38 |     | 28 |     |       |                   |              | Heterogeneity: Chi² = 1.45, df = 2 (P = 0.48); I² = 0% |    |    |    |       |                   |                |     | Test for overall effect: Z = 1.26 (P = 0.21) |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | PCT    |       | Control |       | Weight | Risk Ratio         |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Events | Total | Events  | Total |        | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Corti 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 12     | 62    | 12      | 58    | 43.9%  | 0.94 [0.46, 1.91]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Verduri 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 13     | 88    | 8       | 90    | 28.0%  | 1.66 [0.72, 3.81]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Wang 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 13     | 95    | 8       | 96    | 28.2%  | 1.64 [0.71, 3.78]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 245    |       | 244     |       | 100.0% | 1.34 [0.85, 2.10]  |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 38     |       | 28      |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Heterogeneity: Chi² = 1.45, df = 2 (P = 0.48); I² = 0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 1.26 (P = 0.21)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <b>Balance entre beneficios y riesgos</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| El tratamiento antibiótico guiado por procalcitonina se asocia una menor prescripción de antibióticos y una reducción en la duración de su uso, sin observarse diferencias frente a placebo en la tasa de fracasos terapéuticos, recurrencias, hospitalización o mortalidad.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <b>Calidad global de la evidencia</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| La confianza global con los resultados fue BAJA principalmente debido al diseño de los estudios y a la imprecisión de los resultados.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <b>Uso de recursos y costes</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| No se identificó ninguna referencia relevante para esta pregunta                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <b>Recomendaciones</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| No se sugiere el empleo regular de la procalcitonina para guiar el uso de antibióticos durante la agudización de la EPOC (recomendación débil, calidad de evidencia baja)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |        |       |         |       |        |                    |                    |  |  |                     |     |  |         |  |        |            |  |        |       |        |       |                    |                    |                   |    |    |    |    |       |                   |  |              |    |    |    |    |       |                   |             |    |     |    |     |       |                   |                |     |     |     |     |        |                   |              |    |     |    |     |       |                   |              |                                                        |    |    |    |       |                   |                |     |                                              |     |    |        |                   |                |     |  |     |  |        |                   |              |                                                        |  |     |  |  |  |  |                                                        |                                              |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |

|                         |
|-------------------------|
| <b>Especificaciones</b> |
|-------------------------|

|                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| La procalcitonina es útil para reducir el consumo de antibióticos. No obstante, su mayor coste, su menor disponibilidad y la posibilidad de contar con parámetros clínicos, como el color del esputo, o biomarcadores de mayor accesibilidad como la PCR, no aconsejan su empleo regular para la agudización de la EPOC. |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Pregunta: Determinación de la PCT para guiar la administración de antibióticos en los pacientes con una agudización de la EPOC

| Certainty assessment                 |                    |                    |                |                     |                    |                       | Nº de pacientes            |                  | Efecto                |                                                 | Calidad de la evidencia                                                                        | Importancia |
|--------------------------------------|--------------------|--------------------|----------------|---------------------|--------------------|-----------------------|----------------------------|------------------|-----------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------|-------------|
| Nº de estudios                       | Diseño de estudio  | Riesgo de sesgo    | Inconsistencia | Evidencia indirecta | Imprecisión        | Otras consideraciones | Tratamiento guiado por PCT | placebo          | Relativo (95% CI)     | Absoluto (95% CI)                               |                                                                                                |             |
| Fracaso terapéutico                  |                    |                    |                |                     |                    |                       |                            |                  |                       |                                                 |                                                                                                |             |
| 6                                    | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | serio <sup>b</sup> | ninguno               | 83/469 (17.7%)             | 99/473 (20.9%)   | RR 0.85 (0.66 a 1.09) | 31 menos por 1,000 (de 71 menos a 19 más )      |  BAJA       | CRÍTICO     |
| Mortalidad por cualquier causa       |                    |                    |                |                     |                    |                       |                            |                  |                       |                                                 |                                                                                                |             |
| 10                                   | ensayos aleatorios | no es serio        | no es serio    | no es serio         | serio <sup>b</sup> | ninguno               | 58/772 (7.5%)              | 47/783 (6.0%)    | RR 1.25 (0.87 a 1.78) | 15 más por 1,000 (de 8 menos a 47 más )         |  MODERADA   | CRÍTICO     |
| Duración estancia hospitalaria       |                    |                    |                |                     |                    |                       |                            |                  |                       |                                                 |                                                                                                |             |
| 11                                   | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | no es serio        | ninguno               | 1037                       | 1042             | -                     | MD 0.03 días menos (1.03 menos a 0.97 más )     |  MODERADA   | IMPORTANTE  |
| Prescripción de antibióticos         |                    |                    |                |                     |                    |                       |                            |                  |                       |                                                 |                                                                                                |             |
| 11                                   | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | no es serio        | ninguno               | 436/1048 (41.6%)           | 709/1051 (67.5%) | RR 0.55 (0.42 a 0.72) | 304 menos por 1,000 (de 391 menos a 189 menos ) |  MODERADA   | IMPORTANTE  |
| Duración del tratamiento antibiótico |                    |                    |                |                     |                    |                       |                            |                  |                       |                                                 |                                                                                                |             |
| 8                                    | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | no es serio        | ninguno               | 798                        | 804              | -                     | MD 2.54 days menos (4.27 menos a 0.81 menos )   |  MODERADA | IMPORTANTE  |

| Certainty assessment           |                    |                    |                |                     |                    |                       | Nº de pacientes            |                 | Efecto                |                                           | Calidad de la evidencia                                                                  | Importancia |
|--------------------------------|--------------------|--------------------|----------------|---------------------|--------------------|-----------------------|----------------------------|-----------------|-----------------------|-------------------------------------------|------------------------------------------------------------------------------------------|-------------|
| Nº de estudios                 | Diseño de estudio  | Riesgo de sesgo    | Inconsistencia | Evidencia indirecta | Imprecisión        | Otras consideraciones | Tratamiento guiado por PCT | placebo         | Relativo (95% CI)     | Absoluto (95% CI)                         |                                                                                          |             |
| 7                              | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | serio <sup>b</sup> | ninguno               | 210/535 (39.3%)            | 207/540 (38.3%) | RR 1.02 (0.91 a 1.15) | 8 más por 1,000 (de 34 menos a 57 más )   |  BAJA | IMPORTANTE  |
| Reingreso                      |                    |                    |                |                     |                    |                       |                            |                 |                       |                                           |                                                                                          |             |
| 6                              | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | serio <sup>b</sup> | ninguno               | 91/482 (18.9%)             | 80/486 (16.5%)  | RR 1.15 (0.88 a 1.50) | 25 más por 1,000 (de 20 menos a 82 más )  |  BAJA | IMPORTANTE  |
| Reingreso debido a agudización |                    |                    |                |                     |                    |                       |                            |                 |                       |                                           |                                                                                          |             |
| 3                              | ensayos aleatorios | serio <sup>a</sup> | no es serio    | no es serio         | serio <sup>b</sup> | ninguno               | 38/245 (15.5%)             | 28/244 (11.5%)  | RR 1.34 (0.85 a 2.10) | 39 más por 1,000 (de 17 menos a 126 más ) |  BAJA | IMPORTANTE  |

CI: Intervalo de confianza ; RR: Razón de riesgo; MD: Diferencia media

Explicaciones

a. Ninguno de los estudios presentó un diseño cegado por lo que no se descarta un potencial impacto en los desenlaces subjetivos  
b. Los límites del IC95% no descartan un efecto beneficioso o perjudicial clínicamente relevante.

## PREGUNTA 5

### Pregunta para responder:

#### ¿Se deben prescribir corticoides orales en las agudizaciones?

No se identificó ninguna revisión sistemática (RS) reciente que evaluara directamente la eficacia del tratamiento con corticoesteroides orales en los pacientes con EPOC agudizado.

Una RS Cochrane del año 2014 evaluó la eficacia de los corticoesteroides sistémicos en el tratamiento de las agudizaciones por EPOC. Esta revisión incluye un análisis de subgrupo según los pacientes fueran ambulatorios u hospitalizados. Una guía de práctica clínica posterior sobre el manejo de las exacerbaciones en los pacientes con EPOC que incluyó esta misma pregunta no identificó estudios posteriores así como tampoco una actualización de la literatura hasta 2020. Esta RS identificó 7 ECA en los que se comparó la administración de corticoesteroides orales frente a placebo. Para el propósito de esta pregunta se excluyen los estudios en los que se combinaron las rutas de administración parenteral y oral.

### Revisiones sistemáticas:

1. Walters JAE, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD001288. DOI: 10.1002/14651858.CD001288.pub4.

### Ensayos clínicos aleatorizados:

1. Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. New England Journal of Medicine 2003;348(26):2618-25.
2. Abroug F, Ouanes-Besbes L, Fkih-Hassen M, Ouanes I, Ayed S, Dachraoui F, et al. Prednisone in COPD exacerbation requiring ventilatory support: an open-label randomised evaluation. European Respiratory Journal 2014;43(3):717-24
3. Cordero PJ, Sole A, Benlloch E, Morales P, Vallterra J, Menendez R, et al. A randomized controlled study of prednisone in outpatients with acute exacerbation of COPD. European Respiratory Journal 1996;9 Suppl 23:110s-1s.
4. Davies L, Angus RM, Calverley PMA. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999; 354:456-60.
5. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. American Journal of Respiratory and Critical Care Medicine 2002;165(5):698-703
6. Thompson W, Nielson C, Carvalho P, Charan N, Crowley J. Controlled trial of oral prednisolone in outpatients with acute COPD exacerbation. American Journal of Respiratory and Critical Care Medicine 1996; 154:407-12.
7. Wood-Baker R, Wilkinson J, Pearce M, Ryan G. A double-blind, randomised, placebo-controlled trial of corticosteroids for acute exacerbations of chronic obstructive pulmonary disease [Abstract]. Australian and New Zealand Journal of Medicine 1998; 28:262.

### Fracaso terapéutico

El análisis conjunto de los datos (5 ECAs, 377 pacientes) mostró una reducción significativa favorable al tratamiento con corticosteroides orales (RR 0.42; IC95% 0.22 a 0.81; 168 eventos menos de 226 a 55 menos por 1000 pacientes tratados).  
La confianza con los resultados es alta (ver tabla de resumen de resultados).

**Calidad  
alta**



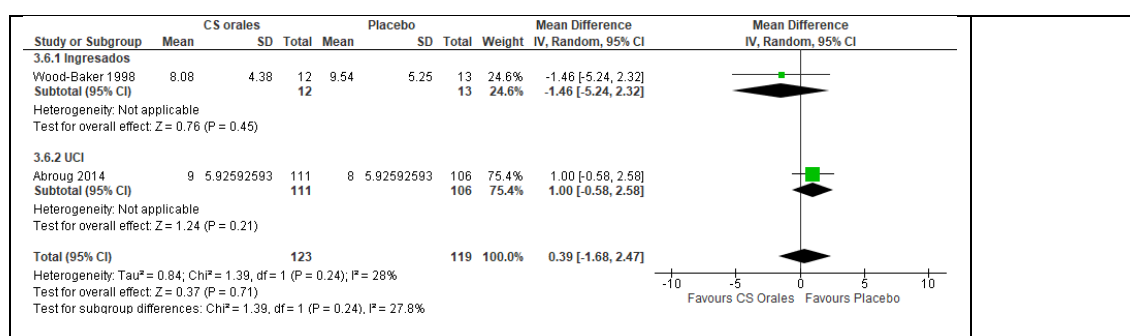
| CS Orales                                                                                                |            | Placebo    |               | Risk Ratio   |        | Risk Ratio               |                     |
|----------------------------------------------------------------------------------------------------------|------------|------------|---------------|--------------|--------|--------------------------|---------------------|
| Study or Subgroup                                                                                        | Events     | Total      | Events        | Total        | Weight | M-H, Random, 95% CI      | M-H, Random, 95% CI |
| <b>3.1.1 Ingresados</b>                                                                                  |            |            |               |              |        |                          |                     |
| Davies 1999                                                                                              | 1          | 29         | 5             | 27           | 8.8%   | 0.19 [0.02, 1.49]        |                     |
| Maltais 2002                                                                                             | 3          | 62         | 8             | 66           | 19.7%  | 0.40 [0.11, 1.44]        |                     |
| Wood-Baker 1998                                                                                          | 1          | 13         | 4             | 13           | 9.0%   | 0.25 [0.03, 1.95]        |                     |
| <b>Subtotal (95% CI)</b>                                                                                 | <b>104</b> | <b>106</b> | <b>106</b>    | <b>37.5%</b> |        | <b>0.31 [0.12, 0.80]</b> |                     |
| Total events                                                                                             | 5          |            | 17            |              |        |                          |                     |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.42, df = 2 (P = 0.81); I <sup>2</sup> = 0%  |            |            |               |              |        |                          |                     |
| Test for overall effect: Z = 2.41 (P = 0.02)                                                             |            |            |               |              |        |                          |                     |
| <b>3.1.3 Ambulatorios</b>                                                                                |            |            |               |              |        |                          |                     |
| Aaron 2003                                                                                               | 19         | 70         | 30            | 70           | 57.2%  | 0.63 [0.40, 1.01]        |                     |
| Thompson 1996                                                                                            | 0          | 13         | 8             | 14           | 5.3%   | 0.06 [0.00, 0.99]        |                     |
| <b>Subtotal (95% CI)</b>                                                                                 | <b>83</b>  | <b>84</b>  | <b>62.5%</b>  |              |        | <b>0.29 [0.03, 2.88]</b> |                     |
| Total events                                                                                             | 19         |            | 38            |              |        |                          |                     |
| Heterogeneity: Tau <sup>2</sup> = 2.05; Chi <sup>2</sup> = 3.02, df = 1 (P = 0.08); I <sup>2</sup> = 67% |            |            |               |              |        |                          |                     |
| Test for overall effect: Z = 1.06 (P = 0.29)                                                             |            |            |               |              |        |                          |                     |
| <b>Total (95% CI)</b>                                                                                    | <b>187</b> | <b>190</b> | <b>100.0%</b> |              |        | <b>0.42 [0.22, 0.81]</b> |                     |
| Total events                                                                                             | 24         |            | 55            |              |        |                          |                     |
| Heterogeneity: Tau <sup>2</sup> = 0.14; Chi <sup>2</sup> = 5.09, df = 4 (P = 0.28); I <sup>2</sup> = 21% |            |            |               |              |        |                          |                     |
| Test for overall effect: Z = 2.58 (P = 0.010)                                                            |            |            |               |              |        |                          |                     |
| Test for subgroup differences: Chi <sup>2</sup> = 0.00, df = 1 (P = 0.96), I <sup>2</sup> = 0%           |            |            |               |              |        |                          |                     |
| <br>Favours CS Orales Favours placebo                                                                    |            |            |               |              |        |                          |                     |

|                                                                                                                                                                                                        |                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| <b>Mortalidad por cualquier causa</b>                                                                                                                                                                  | <b>Calidad moderada</b> |
| En el análisis conjunto de los datos (6 ECAs, 606 pacientes) no mostró diferencias significativas entre el tratamiento con corticosteroides orales y placebo (RR 1.07; IC95% 0.60 a 1.93; 38 eventos). |                         |
| La confianza con los resultados es moderada (ver tabla de resumen de resultados).                                                                                                                      |                         |

| CS Orales                                                                                               |            | Placebo    |               | Risk Ratio |        | Risk Ratio                |                     |
|---------------------------------------------------------------------------------------------------------|------------|------------|---------------|------------|--------|---------------------------|---------------------|
| Study or Subgroup                                                                                       | Events     | Total      | Events        | Total      | Weight | M-H, Random, 95% CI       | M-H, Random, 95% CI |
| <b>3.4.1 Ingresados</b>                                                                                 |            |            |               |            |        |                           |                     |
| Maltais 2002                                                                                            | 1          | 62         | 0             | 66         | 3.4%   | 3.19 [0.13, 76.88]        |                     |
| Wood-Baker 1998                                                                                         | 0          | 14         | 1             | 17         | 3.5%   | 0.40 [0.02, 9.12]         |                     |
| Davies 1999                                                                                             | 1          | 29         | 1             | 27         | 4.7%   | 0.93 [0.06, 14.16]        |                     |
| <b>Subtotal (95% CI)</b>                                                                                | <b>105</b> | <b>110</b> | <b>11.6%</b>  |            |        | <b>1.03 [0.18, 5.80]</b>  |                     |
| Total events                                                                                            | 2          |            | 2             |            |        |                           |                     |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.84, df = 2 (P = 0.66); I <sup>2</sup> = 0% |            |            |               |            |        |                           |                     |
| Test for overall effect: Z = 0.04 (P = 0.97)                                                            |            |            |               |            |        |                           |                     |
| <b>3.4.3 UCI</b>                                                                                        |            |            |               |            |        |                           |                     |
| Abroug 2014                                                                                             | 17         | 111        | 15            | 106        | 83.9%  | 1.08 [0.57, 2.06]         |                     |
| <b>Subtotal (95% CI)</b>                                                                                | <b>111</b> | <b>106</b> | <b>83.9%</b>  |            |        | <b>1.08 [0.57, 2.06]</b>  |                     |
| Total events                                                                                            | 17         |            | 15            |            |        |                           |                     |
| Heterogeneity: Not applicable                                                                           |            |            |               |            |        |                           |                     |
| Test for overall effect: Z = 0.24 (P = 0.81)                                                            |            |            |               |            |        |                           |                     |
| <b>3.4.4 Ambulatorios</b>                                                                               |            |            |               |            |        |                           |                     |
| Thompson 1996                                                                                           | 0          | 13         | 0             | 14         |        | Not estimable             |                     |
| Aaron 2003                                                                                              | 1          | 74         | 1             | 73         | 4.6%   | 0.99 [0.06, 15.48]        |                     |
| <b>Subtotal (95% CI)</b>                                                                                | <b>87</b>  | <b>87</b>  | <b>4.6%</b>   |            |        | <b>0.99 [0.06, 15.48]</b> |                     |
| Total events                                                                                            | 1          |            | 1             |            |        |                           |                     |
| Heterogeneity: Not applicable                                                                           |            |            |               |            |        |                           |                     |
| Test for overall effect: Z = 0.01 (P = 0.99)                                                            |            |            |               |            |        |                           |                     |
| <b>Total (95% CI)</b>                                                                                   | <b>303</b> | <b>303</b> | <b>100.0%</b> |            |        | <b>1.07 [0.60, 1.93]</b>  |                     |
| Total events                                                                                            | 20         |            | 18            |            |        |                           |                     |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.85, df = 4 (P = 0.93); I <sup>2</sup> = 0% |            |            |               |            |        |                           |                     |
| Test for overall effect: Z = 0.23 (P = 0.82)                                                            |            |            |               |            |        |                           |                     |
| Test for subgroup differences: Chi <sup>2</sup> = 0.01, df = 2 (P = 1.00), I <sup>2</sup> = 0%          |            |            |               |            |        |                           |                     |
| <br>Favours CS Orales Favours Placebo                                                                   |            |            |               |            |        |                           |                     |

|                                                                                                                                                                                                     |                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| <b>Recurrencias</b>                                                                                                                                                                                 | <b>Calidad baja</b> |
| El análisis conjunto de los datos (2 ECAs, 199 pacientes) no mostró diferencias significativas entre el tratamiento con corticosteroides orales y placebo (RR 0.78; IC95% 0.35 a 1.76; 39 eventos). |                     |
| La confianza con los resultados es baja (ver tabla de resumen de resultados).                                                                                                                       |                     |

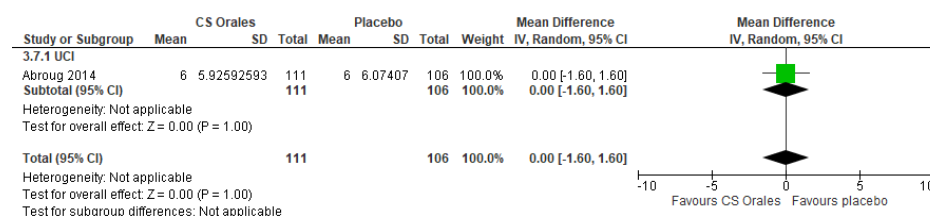
| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">CS Orales</th><th colspan="2">Placebo</th><th rowspan="2">Weight</th><th>Risk Ratio</th><th>Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Random, 95% CI</th><th>M-H, Random, 95% CI</th></tr><tr><td colspan="8"><b>3.3.1 Ingresados</b></td></tr><tr><td>Davies 1999</td><td>9</td><td>29</td><td>7</td><td>27</td><td>48.6%</td><td>1.20 [0.52, 2.76]</td><td rowspan="4"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>29</td><td></td><td>27</td><td>48.6%</td><td>1.20 [0.52, 2.76]</td></tr><tr><td>Total events</td><td>9</td><td></td><td>7</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable<br/>Test for overall effect: Z = 0.42 (P = 0.67)</td></tr><tr><td colspan="8"><b>3.3.2 Ambulatorios</b></td></tr><tr><td>Aaron 2003</td><td>8</td><td>72</td><td>15</td><td>71</td><td>51.4%</td><td>0.53 [0.24, 1.16]</td><td rowspan="4"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>72</td><td></td><td>71</td><td>51.4%</td><td>0.53 [0.24, 1.16]</td></tr><tr><td>Total events</td><td>8</td><td></td><td>15</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable<br/>Test for overall effect: Z = 1.59 (P = 0.11)</td></tr><tr><td>Total (95% CI)</td><td></td><td>101</td><td></td><td>98</td><td>100.0%</td><td>0.78 [0.35, 1.76]</td><td></td></tr><tr><td>Total events</td><td>17</td><td></td><td>22</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="8">Heterogeneity: Tau<sup>2</sup> = 0.17; Chi<sup>2</sup> = 1.98, df = 1 (P = 0.16); I<sup>2</sup> = 49%<br/>Test for overall effect: Z = 0.59 (P = 0.56)<br/>Test for subgroup differences: Chi<sup>2</sup> = 1.95, df = 1 (P = 0.16), I<sup>2</sup> = 48.8%</td></tr></table> |                   |        |         |                   |        |                     | Study or Subgroup   | CS Orales               |                   | Placebo |        | Weight       | Risk Ratio | Risk Ratio   | Events          | Total             | Events          | Total             | M-H, Random, 95% CI | M-H, Random, 95% CI       | <b>3.3.1 Ingresados</b> |      |    |       |                   |  |                   |            | Davies 1999             | 9      | 29     | 7                 | 27 | 48.6% | 1.20 [0.52, 2.76] |                   | Subtotal (95% CI) |  | 29     |                   | 27   | 48.6% | 1.20 [0.52, 2.76]                                                             | Total events | 9    |    | 7                  |  |  |                | Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.42 (P = 0.67) |  |        |                   |  |  |                                                                                                                                | <b>3.3.2 Ambulatorios</b> |  |  |  |  |  |  |  | Aaron 2003 | 8 | 72 | 15 | 71 | 51.4% | 0.53 [0.24, 1.16] |  | Subtotal (95% CI) |  | 72 |  | 71 | 51.4% | 0.53 [0.24, 1.16] | Total events | 8 |  | 15 |  |  |  | Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.59 (P = 0.11) |  |  |  |  |  |  | Total (95% CI) |  | 101 |  | 98 | 100.0% | 0.78 [0.35, 1.76] |  | Total events | 17 |  | 22 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.17; Chi <sup>2</sup> = 1.98, df = 1 (P = 0.16); I <sup>2</sup> = 49%<br>Test for overall effect: Z = 0.59 (P = 0.56)<br>Test for subgroup differences: Chi <sup>2</sup> = 1.95, df = 1 (P = 0.16), I <sup>2</sup> = 48.8% |  |  |  |  |  |  |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------|---------|-------------------|--------|---------------------|---------------------|-------------------------|-------------------|---------|--------|--------------|------------|--------------|-----------------|-------------------|-----------------|-------------------|---------------------|---------------------------|-------------------------|------|----|-------|-------------------|--|-------------------|------------|-------------------------|--------|--------|-------------------|----|-------|-------------------|-------------------|-------------------|--|--------|-------------------|------|-------|-------------------------------------------------------------------------------|--------------|------|----|--------------------|--|--|----------------|-------------------------------------------------------------------------------|--|--------|-------------------|--|--|--------------------------------------------------------------------------------------------------------------------------------|---------------------------|--|--|--|--|--|--|--|------------|---|----|----|----|-------|-------------------|--|-------------------|--|----|--|----|-------|-------------------|--------------|---|--|----|--|--|--|-------------------------------------------------------------------------------|--|--|--|--|--|--|----------------|--|-----|--|----|--------|-------------------|--|--------------|----|--|----|--|--|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|--|
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | CS Orales         |        | Placebo |                   | Weight | Risk Ratio          |                     | Risk Ratio              |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Events            | Total  | Events  | Total             |        | M-H, Random, 95% CI | M-H, Random, 95% CI |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <b>3.3.1 Ingresados</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Davies 1999                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 9                 | 29     | 7       | 27                | 48.6%  | 1.20 [0.52, 2.76]   |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   | 29     |         | 27                | 48.6%  | 1.20 [0.52, 2.76]   |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 9                 |        | 7       |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.42 (P = 0.67)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <b>3.3.2 Ambulatorios</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Aaron 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 8                 | 72     | 15      | 71                | 51.4%  | 0.53 [0.24, 1.16]   |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   | 72     |         | 71                | 51.4%  | 0.53 [0.24, 1.16]   |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 8                 |        | 15      |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 1.59 (P = 0.11)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                   | 101    |         | 98                | 100.0% | 0.78 [0.35, 1.76]   |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 17                |        | 22      |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.17; Chi <sup>2</sup> = 1.98, df = 1 (P = 0.16); I <sup>2</sup> = 49%<br>Test for overall effect: Z = 0.59 (P = 0.56)<br>Test for subgroup differences: Chi <sup>2</sup> = 1.95, df = 1 (P = 0.16), I <sup>2</sup> = 48.8%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <b>Tasa de recurrencias</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |        |         |                   |        |                     |                     | <b>Calidad moderada</b> |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <p>Un ECAs, 143 pacientes mostraron una reducción significativa favorable a los corticoesteroides orales respecto a placebo en la tasa de recaídas. (HR 0.78; IC95% 0.61 a 0.99).</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <table><tr><th rowspan="2">Study or Subgroup</th><th rowspan="2">log[Hazard ratio]</th><th rowspan="2">SE</th><th rowspan="2">Weight</th><th colspan="2">Hazard ratio</th><th colspan="2">Hazard ratio</th></tr><tr><th>IV, Fixed, 95% CI</th><th></th><th>IV, Fixed, 95% CI</th><th></th></tr><tr><td colspan="8"><b>3.2.2 Ambulatorios</b></td></tr><tr><td>Aaron 2003</td><td>-0.2518</td><td>0.1251</td><td>100.0%</td><td>0.78 [0.61, 0.99]</td><td></td><td></td><td rowspan="4"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.78 [0.61, 0.99]</td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable<br/>Test for overall effect: Z = 2.01 (P = 0.04)</td></tr><tr><td>Total (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.78 [0.61, 0.99]</td><td></td><td></td></tr><tr><td colspan="8">Heterogeneity: Not applicable<br/>Test for overall effect: Z = 2.01 (P = 0.04)<br/>Test for subgroup differences: Not applicable</td></tr></table>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                   |        |         |                   |        |                     |                     | Study or Subgroup       | log[Hazard ratio] | SE      | Weight | Hazard ratio |            | Hazard ratio |                 | IV, Fixed, 95% CI |                 | IV, Fixed, 95% CI |                     | <b>3.2.2 Ambulatorios</b> |                         |      |    |       |                   |  |                   | Aaron 2003 | -0.2518                 | 0.1251 | 100.0% | 0.78 [0.61, 0.99] |    |       |                   | Subtotal (95% CI) |                   |  | 100.0% | 0.78 [0.61, 0.99] |      |       | Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.01 (P = 0.04) |              |      |    |                    |  |  | Total (95% CI) |                                                                               |  | 100.0% | 0.78 [0.61, 0.99] |  |  | Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.01 (P = 0.04)<br>Test for subgroup differences: Not applicable |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | log[Hazard ratio] | SE     | Weight  | Hazard ratio      |        | Hazard ratio        |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                   |        |         | IV, Fixed, 95% CI |        | IV, Fixed, 95% CI   |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <b>3.2.2 Ambulatorios</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Aaron 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | -0.2518           | 0.1251 | 100.0%  | 0.78 [0.61, 0.99] |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |        | 100.0%  | 0.78 [0.61, 0.99] |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.01 (P = 0.04)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                   |        | 100.0%  | 0.78 [0.61, 0.99] |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.01 (P = 0.04)<br>Test for subgroup differences: Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <b>Calidad de vida - Chronic Respiratory Disease Questionnaire (CRQ)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                   |        |         |                   |        |                     |                     | <b>Calidad moderada</b> |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <p>Un ECA (147 pacientes) no muestra diferencias significativas entre el tratamiento con corticosteroides orales y placebo en el estado salud medido con el cuestionario CRQ (Chronic Respiratory Disease Questionnaire) (MD 0.38 puntos más; IC95% 0.68 menos a 1.44 puntos más).</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="3">CS Orales</th><th colspan="3">Placebo</th><th colspan="2">Mean Difference</th><th colspan="2">Mean Difference</th></tr><tr><th>Mean</th><th>SD</th><th>Total</th><th>Mean</th><th>SD</th><th>Total</th><th>IV, Fixed, 95% CI</th><th></th><th>IV, Fixed, 95% CI</th><th></th></tr><tr><td colspan="11"><b>3.5.1 Ingresados</b></td></tr><tr><td>Aaron 2003</td><td>1.42</td><td>4.43</td><td>74</td><td>1.04</td><td>1.47</td><td>73</td><td>0.38 [-0.68, 1.44]</td><td></td><td></td><td rowspan="2"></td></tr><tr><td colspan="10"></td></tr></table>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                   |        |         |                   |        |                     |                     | Study or Subgroup       | CS Orales         |         |        | Placebo      |            |              | Mean Difference |                   | Mean Difference |                   | Mean                | SD                        | Total                   | Mean | SD | Total | IV, Fixed, 95% CI |  | IV, Fixed, 95% CI |            | <b>3.5.1 Ingresados</b> |        |        |                   |    |       |                   |                   |                   |  |        | Aaron 2003        | 1.42 | 4.43  | 74                                                                            | 1.04         | 1.47 | 73 | 0.38 [-0.68, 1.44] |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | CS Orales         |        |         | Placebo           |        |                     | Mean Difference     |                         | Mean Difference   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Mean              | SD     | Total   | Mean              | SD     | Total               | IV, Fixed, 95% CI   |                         | IV, Fixed, 95% CI |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <b>3.5.1 Ingresados</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| Aaron 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.42              | 4.43   | 74      | 1.04              | 1.47   | 73                  | 0.38 [-0.68, 1.44]  |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <b>Duración estancia hospitalaria</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                   |        |         |                   |        |                     |                     | <b>Calidad moderada</b> |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |
| <p>En el análisis conjunto de los datos (2 ECAs, 242 pacientes) no mostró diferencias significativas entre el tratamiento con corticosteroides orales y placebo (MD 0.39 días más; IC95% 1.68 menos a 2.47 días más).</p> <p>La confianza con los resultados es moderada (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                   |        |         |                   |        |                     |                     |                         |                   |         |        |              |            |              |                 |                   |                 |                   |                     |                           |                         |      |    |       |                   |  |                   |            |                         |        |        |                   |    |       |                   |                   |                   |  |        |                   |      |       |                                                                               |              |      |    |                    |  |  |                |                                                                               |  |        |                   |  |  |                                                                                                                                |                           |  |  |  |  |  |  |  |            |   |    |    |    |       |                   |  |                   |  |    |  |    |       |                   |              |   |  |    |  |  |  |                                                                               |  |  |  |  |  |  |                |  |     |  |    |        |                   |  |              |    |  |    |  |  |  |  |                                                                                                                                                                                                                                                               |  |  |  |  |  |  |  |  |



## Duración de la ventilación mecánica

Un ECA, 117 pacientes, no mostró diferencias significativas entre el tratamiento con corticosteroides orales y placebo (MD 0; IC95% 1.6 días menos a 1.6 días más).

La confianza con los resultados es moderada (ver tabla de resumen de resultados).

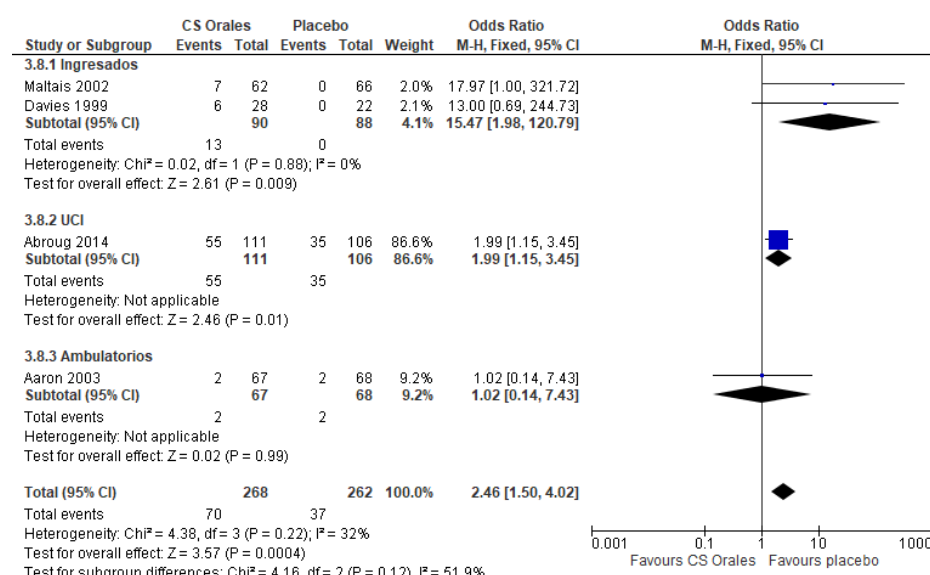


**Calidad  
baja**

## Efectos indeseados - hiperglicemia

En el análisis conjunto de los datos (4 ECAs, 530 pacientes) mostró un incremento significativo de los pacientes con hiperglicemia entre el tratamiento con corticosteroides orales y placebo (RR 2.46; IC95% 1.50 a 4.02; 147 eventos más de 57 a 257 más por 1000 pacientes tratados).

La confianza con los resultados es moderada (ver tabla de resumen de resultados).



**Calidad  
moderada**

## Balance entre beneficios y riesgos

Los corticoides orales reducen el fracaso terapéutico, la tasa de recurrencias sin impacto en la calidad de vida relacionada con la salud, la duración de la estancia hospitalaria, la duración de la ventilación mecánica o la mortalidad. Por el contrario si que se aprecia un incremento significativo de los pacientes con hiperglicemia.

|                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Existen muy pocos datos sobre la eficacia de los corticoides orales en agudizaciones muy graves que cursen con acidosis respiratoria.                                                                                                                                                                                                                                         |
| <b>Calidad global de la evidencia</b>                                                                                                                                                                                                                                                                                                                                         |
| La confianza global con los resultados fue moderada principalmente debido a la imprecisión de los resultados de mortalidad.                                                                                                                                                                                                                                                   |
| <b>Uso de recursos y costes</b>                                                                                                                                                                                                                                                                                                                                               |
| No se identificó ninguna referencia relevante para esta pregunta                                                                                                                                                                                                                                                                                                              |
| <b>Recomendaciones</b>                                                                                                                                                                                                                                                                                                                                                        |
| <p><b>En pacientes ambulatorios:</b><br/>Se sugiere el uso de corticoides orales en pacientes con agudización moderada (recomendación débil, calidad de evidencia moderada)</p> <p><b>En pacientes ingresados:</b><br/>Se recomienda el uso de corticoides orales en pacientes con una agudización grave de la EPOC (recomendación fuerte, calidad de evidencia moderada)</p> |
| <b>Especificaciones</b>                                                                                                                                                                                                                                                                                                                                                       |
| <p>La dosis recomendada de corticoides orales es de 0,5 mg/kg/día de prednisona o equivalente, durante un máximo de 5 días en agudizaciones moderadas y durante un máximo de 12 días en agudizaciones graves.</p> <p>La vía parenteral es preferible para las agudizaciones muy graves</p>                                                                                    |

Pregunta: ¿Se deben prescribir corticoides orales en las agudizaciones de la EPOC?

| Certainty assessment                                                    |                    |                    |                          |                     |                    |                       | Nº de pacientes     |                | Efecto                |                                               | Certainty        | Importancia |
|-------------------------------------------------------------------------|--------------------|--------------------|--------------------------|---------------------|--------------------|-----------------------|---------------------|----------------|-----------------------|-----------------------------------------------|------------------|-------------|
| Nº de estudios                                                          | Diseño de estudio  | Riesgo de sesgo    | Inconsistencia           | Evidencia indirecta | Imprecisión        | Otras consideraciones | Oral corticosteroid | placebo        | Relativo (95% CI)     | Absoluto (95% CI)                             |                  |             |
| Fracaso terapéutico                                                     |                    |                    |                          |                     |                    |                       |                     |                |                       |                                               |                  |             |
| 5                                                                       | ensayos aleatorios | no es serio        | no es serio              | no es serio         | no es serio        | ninguno               | 24/187 (12.8%)      | 55/190 (28.9%) | RR 0.42 (0.22 a 0.81) | 168 menos por 1000 (de 226 menos a 55 menos ) | ⊕⊕⊕⊕<br>ALTA     | CRÍTICO     |
| Mortalidad por cualquier causa                                          |                    |                    |                          |                     |                    |                       |                     |                |                       |                                               |                  |             |
| 6                                                                       | ensayos aleatorios | no es serio        | no es serio              | no es serio         | serio <sup>b</sup> | ninguno               | 20/303 (6.6%)       | 18/303 (5.9%)  | RR 1.07 (0.60 a 1.93) | 4 más por 1000 (de 24 menos a 55 más )        | ⊕⊕⊕○<br>MODERADA | CRÍTICO     |
| Tasa de recaídas (seguimiento a 30 días)                                |                    |                    |                          |                     |                    |                       |                     |                |                       |                                               |                  |             |
| 1                                                                       | ensayos aleatorios | no es serio        | no es serio <sup>a</sup> | no es serio         | serio <sup>b</sup> | ninguno               | 8/72 (11.1%)        | 15/71 (21.1%)  | HR 0.78 (0.61 a 0.99) | 42 menos por 1000 (de 76 menos a 2 menos )    | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Recaídas                                                                |                    |                    |                          |                     |                    |                       |                     |                |                       |                                               |                  |             |
| 2                                                                       | ensayos aleatorios | no es serio        | serio <sup>c</sup>       | no es serio         | serio <sup>b</sup> | ninguno               | 17/101 (16.8%)      | 22/98 (22.4%)  | RR 0.78 (0.35 a 1.76) | 49 menos por 1000 (de 146 menos a 171 más )   | ⊕⊕○○<br>BAJA     | IMPORTANTE  |
| Chronic Respiratory Disease Questionnaire (CRQ) (cambio respecto basal) |                    |                    |                          |                     |                    |                       |                     |                |                       |                                               |                  |             |
| 1                                                                       | ensayos aleatorios | no es serio        | no es serio <sup>a</sup> | no es serio         | serio <sup>d</sup> | ninguno               | 74                  | 73             | -                     | MD 0.38 más (0.68 menos a 1.44 más )          | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Duración estancia hospitalaria (días)                                   |                    |                    |                          |                     |                    |                       |                     |                |                       |                                               |                  |             |
| 2                                                                       | ensayos aleatorios | no es serio        | no es serio              | no es serio         | serio <sup>d</sup> | ninguno               | 123                 | 119            | -                     | MD 0.39 más (1.68 menos a 2.47 más )          | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |
| Duración ventilación mecánica (días)                                    |                    |                    |                          |                     |                    |                       |                     |                |                       |                                               |                  |             |
| 1                                                                       | ensayos aleatorios | serio <sup>e</sup> | no es serio <sup>a</sup> | no es serio         | serio <sup>d</sup> | ninguno               | 111                 | 106            | -                     | MD 0 (1.6 menos a 1.6 más )                   | ⊕⊕○○<br>BAJA     | IMPORTANTE  |

Efectos indeseados - hiperglicemia (seguimiento a 30 días)

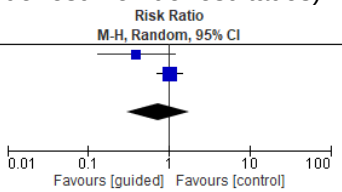
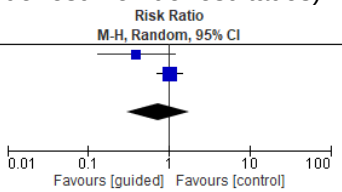
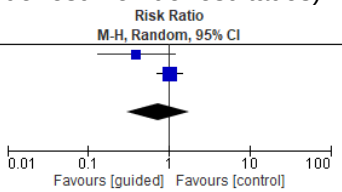
| Certainty assessment |                    |                 |                    |                     |             |                       | Nº de pacientes     |                | Efecto                |                                         | Certainty        | Importancia |
|----------------------|--------------------|-----------------|--------------------|---------------------|-------------|-----------------------|---------------------|----------------|-----------------------|-----------------------------------------|------------------|-------------|
| Nº de estudios       | Diseño de estudio  | Riesgo de sesgo | Inconsistencia     | Evidencia indirecta | Imprecisión | Otras consideraciones | Oral corticosteroid | placebo        | Relativo (95% CI)     | Absoluto (95% CI)                       |                  |             |
| 4                    | ensayos aleatorios | no es serio     | serio <sup>c</sup> | no es serio         | no es serio | ninguno               | 70/268 (26.1%)      | 37/262 (14.1%) | OR 2.46 (1.50 a 4.02) | 147 más por 1000 (de 57 más a 257 más ) | ⊕⊕⊕○<br>MODERADA | IMPORTANTE  |

CI: Intervalo de confianza ; RR: Razón de riesgo; HR: Razón de riesgos instantáneos; MD: Diferencia media; OR: Razón de momios

Explicaciones

- a. Un único estudio
- b. Escaso número de eventos; los límites del IC95% indican un efecto beneficioso o perjudicial relevante
- c. Variabilidad significativa de los resultados entre los distintos estudios incluidos
- d. Los límites inferior o superior del IC95% superan la diferencia mínima clínicamente relevante
- e. Estudio abierto; no se puede descartar un potencial riesgo de sesgo en la evaluación de un desenlace subjetivo

PREGUNTA 6

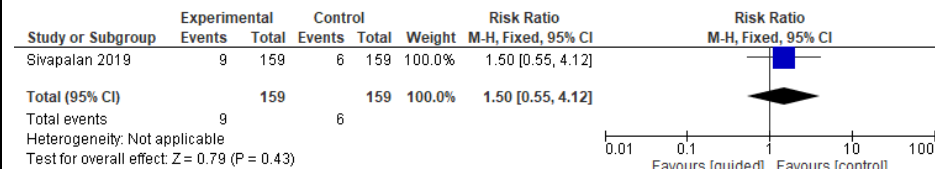
| <p><b>Pregunta para responder:</b><br/><b>¿La determinación de los eosinófilos, es útil para guiar la administración de corticosteroides orales en los pacientes con una agudización de la EPOC?</b></p> <p>Para responder a la pregunta de la determinación de eosinófilos para guiar el tratamiento con corticosteroides orales se identificaron dos revisiones, una de ellas narrativa (Bafadhel 2014 y Bruselle 2018). Estas dos revisiones identificaron un estudio que evaluó la relación entre la concentración de eosinófilos y los resultados clínicos del tratamiento con corticosteroides orales (Bafadhel 2012). Posteriormente se identificó un ECA adicional (Sivapalan 2019).</p> <p><b>Revisiones sistemáticas:</b></p> <ol style="list-style-type: none"><li>1. Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. Eur Respir J 2014; 44: 789–91</li><li>2. Brusselle G, Pavord ID, Landis S, Pascoe S, Lettis S, Morjaria N, Barnes N, Hilton E. Blood eosinophil levels as a biomarker in COPD. Respir Med. 2018 May;138:21</li></ol> <p><b>Ensayos clínicos aleatorizados:</b></p> <ol style="list-style-type: none"><li>1. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2012; 186: 48–55.</li><li>2. Sivapalan P, Lapperre TS, Janner J, Laub RR, Moberg M, Bech CS, Eklöf J, Holm FS, Armbruster K, Sivapalan P, Mosbech C, Ali AKM, Seersholm N, Wilcke JT, Brøndum E, Sonne TP, Rønholt F, Andreassen HF, Ulrik CS, Vestbo J, Jensen JS. Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial. Lancet Respir Med. 2019 Aug;7(8):699-709</li></ol> <p>Los dos estudios aleatorizaron los pacientes a una estrategia de tratamiento guiada por la determinación de eosinófilos en sangre. En el primer estudio el grupo de tratamiento guiado recibió 30mg de prednisolona oral o placebo según el resultado de los eosinófilos en sangre (más del 2% o igual o menor al 2%). El grupo de tratamiento estándar recibió 30mg de prednisolona independientemente de los resultados. Todos los pacientes recibieron además tratamiento con antibióticos de amplio espectro (Bafadhel 2012).</p> <p>En el segundo estudio evaluó una estrategia de reducción del tratamiento con corticosteroides de modo que todos los pacientes recibieron 80 mg de metilprednisolona IV, durante los 4 siguientes días el grupo de tratamiento guiado sólo recibió 37,5 mg de prednisolona oral los días con una determinación de eosinófilos &gt;3X10<sup>9</sup>/L. El grupo estándar recibió prednisolona oral los 4 días siguientes, independientemente de los resultados de eosinófilos en sangre (Sivapalan 2019).</p> |                            |                   |              |       |         |             |              |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
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| <p><b>Tratamiento con antibióticos guiado por eosinófilos vs tratamiento estándar</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                            |                   |              |       |         |             |              |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <p><b>Fracaso terapéutico</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                            |                   |              |       |         |             |              |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <p>En el análisis conjunto de los datos (2 ECAs, 427 pacientes) no mostró diferencias significativas respecto al fracaso terapéutico entre la estrategia guiada por la determinación de eosinófilos en sangre o el criterio habitual (RR 0.73; IC95% 0.30 a 1.80; 97 eventos).</p> <p>La confianza con los resultados es baja (ver tabla de resumen de resultados).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <p><b>Calidad baja</b></p> |                   |              |       |         |             |              |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Experimental</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th><th rowspan="2">M-H, Random, 95% CI</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Random</th><th>95% CI</th></tr><tr><td>Bafadhel 2012</td><td>4</td><td>55</td><td>10</td><td>54</td><td>35.1%</td><td>0.39</td><td>[0.13, 1.18]</td><td rowspan="4"></td></tr><tr><td>Sivapalan 2019</td><td>42</td><td>159</td><td>41</td><td>159</td><td>64.9%</td><td>1.02</td><td>[0.71, 1.48]</td></tr><tr><td>Total (95% CI)</td><td></td><td>214</td><td></td><td>213</td><td>100.0%</td><td>0.73</td><td>[0.30, 1.80]</td></tr><tr><td>Total events</td><td>46</td><td></td><td>51</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="9">Heterogeneity: Tau<sup>2</sup> = 0.29; Chi<sup>2</sup> = 2.67, df = 1 (P = 0.10); I<sup>2</sup> = 62%</td></tr><tr><td colspan="9">Test for overall effect: Z = 0.68 (P = 0.50)</td></tr></table>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                            | Study or Subgroup | Experimental |       | Control |             | Weight       | Risk Ratio                                                                           |  | M-H, Random, 95% CI | Events | Total | Events | Total | M-H, Random | 95% CI | Bafadhel 2012 | 4 | 55 | 10 | 54 | 35.1% | 0.39 | [0.13, 1.18] |  | Sivapalan 2019 | 42 | 159 | 41 | 159 | 64.9% | 1.02 | [0.71, 1.48] | Total (95% CI) |  | 214 |  | 213 | 100.0% | 0.73 | [0.30, 1.80] | Total events | 46 |  | 51 |  |  |  |  | Heterogeneity: Tau <sup>2</sup> = 0.29; Chi <sup>2</sup> = 2.67, df = 1 (P = 0.10); I <sup>2</sup> = 62% |  |  |  |  |  |  |  |  | Test for overall effect: Z = 0.68 (P = 0.50) |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Experimental               |                   | Control      |       | Weight  | Risk Ratio  |              | M-H, Random, 95% CI                                                                  |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Events                     | Total             | Events       | Total |         | M-H, Random | 95% CI       |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Bafadhel 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 4                          | 55                | 10           | 54    | 35.1%   | 0.39        | [0.13, 1.18] |  |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Sivapalan 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 42                         | 159               | 41           | 159   | 64.9%   | 1.02        | [0.71, 1.48] |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                            | 214               |              | 213   | 100.0%  | 0.73        | [0.30, 1.80] |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 46                         |                   | 51           |       |         |             |              |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.29; Chi <sup>2</sup> = 2.67, df = 1 (P = 0.10); I <sup>2</sup> = 62%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                            |                   |              |       |         |             |              |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 0.68 (P = 0.50)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                            |                   |              |       |         |             |              |                                                                                      |  |                     |        |       |        |       |             |        |               |   |    |    |    |       |      |              |                                                                                      |                |    |     |    |     |       |      |              |                |  |     |  |     |        |      |              |              |    |  |    |  |  |  |  |                                                                                                          |  |  |  |  |  |  |  |  |                                              |  |  |  |  |  |  |  |  |

**Mortalidad por cualquier causa**

Un ECA (318 pacientes) no muestra una diferencia significativa en la mortalidad entre las dos estrategias (RR 1.50; IC95% 0.55 a 4.12; 15 eventos).

La confianza con los resultados es baja (ver tabla de resumen de resultados).

**Calidad  
baja**

**Reingreso por EPOC agudizado o muerte (día 30)**

Un ECA (318 pacientes) no muestra una diferencia significativa en un desenlace combinado de re-hospitalización por EPOC y muerte a los 30 días de seguimiento (RR 1.44; IC95% 0.93 a 2.24; 56 eventos).

La confianza con los resultados es baja (ver tabla de resumen de resultados).

**Calidad  
baja**

**Pacientes con infecciones que requirieron tratamiento con antibióticos (día 90)**

Un ECA (318 pacientes) no muestra una diferencia significativa en el número de pacientes con infecciones que requirieron tratamiento con antibióticos a los 30 días de seguimiento (RR 0.81; IC95% 0.61 a 1.07; 123 eventos).

La confianza con los resultados es baja (ver tabla de resumen de resultados).

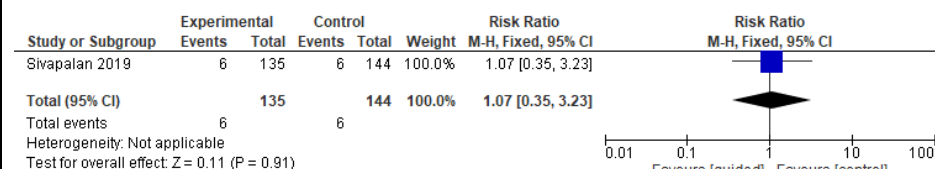
**Calidad  
baja**

**Diagnóstico de diabetes**

Un ECA (318 pacientes) no muestra una diferencia significativa en el número de pacientes con un nuevo diagnóstico de diabetes entre las dos estrategias (RR 1.07; IC95% 0.35 a 3.23; 12 eventos).

La confianza con los resultados es baja (ver tabla de resumen de resultados).

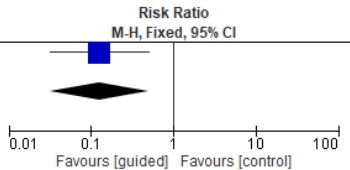
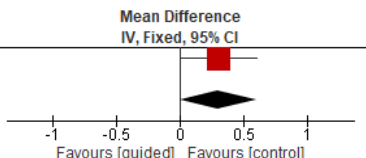
**Calidad  
baja**

**Empeoramiento del control de la diabetes**

En un ECA (318 pacientes) la estrategia guiada por la determinación de eosinófilos en sangre muestra una reducción significativa en el número de pacientes con empeoramiento del control de la diabetes existente (RR 0.13; IC95% 0.03 a 0.49; 12 eventos).

**Calidad  
baja**



| La confianza con los resultados es baja (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------------------|-------------------|--------------------|---------|--------------------|--------------------|-----------------|--|-----------------|-----------------|-------|--------|-------|--------------------|--------------------|----------------|-----|--------|--------|--------------------|--------|-------------------|--|----------------|----------------|--|--------|--------------------|----|--------|-------------------|-------------------------------|--|--------------|---|--|----|--|--|----------------------------------------------|--|--|-------------------------------|--|--|--|--|--|--|--|--|-----------------------------------------------|--|--|--|--|--|--|--|--|--|
| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Experimental</th><th colspan="2">Control</th><th rowspan="2">Weight</th><th colspan="2">Risk Ratio</th><th rowspan="2">Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Fixed, 95% CI</th><th>M-H, Fixed, 95% CI</th></tr><tr><td>Sivapalan 2019</td><td>2</td><td>24</td><td>10</td><td>15</td><td>100.0%</td><td>0.13 [0.03, 0.49]</td><td></td><td></td></tr><tr><td>Total (95% CI)</td><td></td><td>24</td><td></td><td>15</td><td>100.0%</td><td>0.13 [0.03, 0.49]</td><td></td><td></td></tr><tr><td>Total events</td><td>2</td><td></td><td>10</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td colspan="9">Heterogeneity: Not applicable</td></tr><tr><td colspan="9">Test for overall effect: Z = 2.97 (P = 0.003)</td></tr></table>  |                 | Study or Subgroup | Experimental      |                    | Control |                    | Weight             | Risk Ratio      |  | Risk Ratio      | Events          | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | Sivapalan 2019 | 2   | 24     | 10     | 15                 | 100.0% | 0.13 [0.03, 0.49] |  |                | Total (95% CI) |  | 24     |                    | 15 | 100.0% | 0.13 [0.03, 0.49] |                               |  | Total events | 2 |  | 10 |  |  |                                              |  |  | Heterogeneity: Not applicable |  |  |  |  |  |  |  |  | Test for overall effect: Z = 2.97 (P = 0.003) |  |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Experimental    |                   | Control           |                    | Weight  | Risk Ratio         |                    | Risk Ratio      |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Events          | Total             | Events            | Total              |         | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Sivapalan 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 2               | 24                | 10                | 15                 | 100.0%  | 0.13 [0.03, 0.49]  |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                 | 24                |                   | 15                 | 100.0%  | 0.13 [0.03, 0.49]  |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2               |                   | 10                |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 2.97 (P = 0.003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| <b>Chronic Respiratory Disease Questionnaire (CRQ)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                 |                   | Calidad moderada  |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Un ECA (109 pacientes) no muestra una reducción significativa entre las dos estrategias en el estado salud medido con el cuestionario CRQ (Chronic Respiratory Disease Questionnaire) MD 0.3 puntos más; IC95% 0 a 0.6 puntos más).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| La confianza con los resultados es moderada (ver tabla de resumen de resultados).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| <table><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">Mean Difference</th><th rowspan="2">SE</th><th rowspan="2">Weight</th><th colspan="2">Mean Difference</th><th rowspan="2">Mean Difference</th></tr><tr><th colspan="4"></th><th>IV, Fixed, 95% CI</th><th>IV, Fixed, 95% CI</th></tr><tr><td>Bafadhel 2012</td><td>0.3</td><td>0.1531</td><td>100.0%</td><td>0.30 [-0.00, 0.60]</td><td></td><td></td><td></td></tr><tr><td>Total (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.30 [-0.00, 0.60]</td><td></td><td></td><td></td></tr><tr><td colspan="8">Heterogeneity: Not applicable</td></tr><tr><td colspan="8">Test for overall effect: Z = 1.96 (P = 0.05)</td></tr></table>                                                                                                                                                              |                 |                   | Study or Subgroup | Mean Difference    |         | SE                 | Weight             | Mean Difference |  | Mean Difference |                 |       |        |       | IV, Fixed, 95% CI  | IV, Fixed, 95% CI  | Bafadhel 2012  | 0.3 | 0.1531 | 100.0% | 0.30 [-0.00, 0.60] |        |                   |  | Total (95% CI) |                |  | 100.0% | 0.30 [-0.00, 0.60] |    |        |                   | Heterogeneity: Not applicable |  |              |   |  |    |  |  | Test for overall effect: Z = 1.96 (P = 0.05) |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Mean Difference |                   |                   | SE                 | Weight  |                    |                    | Mean Difference |  |                 | Mean Difference |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                 |                   |                   |                    |         | IV, Fixed, 95% CI  | IV, Fixed, 95% CI  |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Bafadhel 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.3             | 0.1531            | 100.0%            | 0.30 [-0.00, 0.60] |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                 |                   | 100.0%            | 0.30 [-0.00, 0.60] |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Heterogeneity: Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Test for overall effect: Z = 1.96 (P = 0.05)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| <b>Balance entre beneficios y riesgos</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| En general no se detectaron diferencias significativas entre las dos estrategias respecto al fracaso terapéutico, reingresos, mortalidad o estado de salud. Sin embargo, un estudio diseñado para reducir el uso de corticosteroides orales en aquellos pacientes con un valor bajo de eosinófilos en sangre mostró un mejor control de los pacientes con diabetes. Este estudio muestra que el grupo que siguió una estrategia guiada recibió una menor dosis de corticosteroides orales (en el seguimiento a 5, 30 y 90 días).                                                                                                                                                                                                                                                                                                                                                                                                                         |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| La determinación de eosinófilos en sangre como estrategia orientada a reducir el tratamiento con corticosteroides orales en los pacientes con agudizaciones de la EPOC consigue reducir la dosis total sin diferencias significativas en el control de la EPOC.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| <b>Calidad global de la evidencia</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| La confianza global con los resultados fue baja principalmente debido a la variabilidad e imprecisión de los resultados.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| <b>Uso de recursos y costes</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| No se identificó ninguna referencia relevante para esta pregunta                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| <b>Recomendaciones</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| Se recomienda administrar el uso de corticoides orales en pacientes con recuento de eosinófilos ≥ 300 células/mm <sup>3</sup> (recomendación débil, calidad de evidencia baja).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| <b>Especificaciones</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |
| La eficacia de los corticoides orales en las agudizaciones de la EPOC es mayor en pacientes con recuento de eosinófilos ≥ 300 células/mm <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                 |                   |                   |                    |         |                    |                    |                 |  |                 |                 |       |        |       |                    |                    |                |     |        |        |                    |        |                   |  |                |                |  |        |                    |    |        |                   |                               |  |              |   |  |    |  |  |                                              |  |  |                               |  |  |  |  |  |  |  |  |                                               |  |  |  |  |  |  |  |  |  |

Pregunta: ¿La determinación de los eosinófilos, es útil para guiar la administración de corticosteroides orales en los pacientes con una agudización de la EPOC?

| Certainty assessment                                                            |                    |                    |                          |                     |                        |                       | Nº de pacientes                           |                   | Efecto                |                                                | Certainty                                                                                      | Importancia |
|---------------------------------------------------------------------------------|--------------------|--------------------|--------------------------|---------------------|------------------------|-----------------------|-------------------------------------------|-------------------|-----------------------|------------------------------------------------|------------------------------------------------------------------------------------------------|-------------|
| Nº de estudios                                                                  | Diseño de estudio  | Riesgo de sesgo    | Inconsistencia           | Evidencia indirecta | Imprecisión            | Otras consideraciones | la determinación de eosinófilos en sangre | criterio habitual | Relativo (95% CI)     | Absoluto (95% CI)                              |                                                                                                |             |
| Fracaso terapéutico                                                             |                    |                    |                          |                     |                        |                       |                                           |                   |                       |                                                |                                                                                                |             |
| 2                                                                               | ensayos aleatorios | no es serio        | serio <sup>a</sup>       | no es serio         | serio <sup>b</sup>     | ninguno               | 46/214 (21.5%)                            | 51/213 (23.9%)    | RR 0.73 (0.30 a 1.80) | 50 más por 1000 (de 70 menos a 170 más )       |  BAJA       | CRÍTICO     |
| Mortalidad por cualquier causa                                                  |                    |                    |                          |                     |                        |                       |                                           |                   |                       |                                                |                                                                                                |             |
| 1                                                                               | ensayos aleatorios | no es serio        | no es serio <sup>c</sup> | no es serio         | muy serio <sup>e</sup> | ninguno               | 9/159 (5.7%)                              | 6/159 (3.8%)      | RR 1.50 (0.55 a 4.12) | 19 más por 1000 (de 17 menos a 118 más )       |  BAJA       | CRÍTICO     |
| Reingreso por EPOC agudizado o muerte (día 30)                                  |                    |                    |                          |                     |                        |                       |                                           |                   |                       |                                                |                                                                                                |             |
| 1                                                                               | ensayos aleatorios | no es serio        | no es serio <sup>c</sup> | serio <sup>d</sup>  | serio <sup>b</sup>     | ninguno               | 39/159 (24.5%)                            | 27/159 (17.0%)    | RR 1.44 (0.93 a 2.24) | 75 más por 1000 (de 12 menos a 211 más )       |  BAJA       | IMPORTANTE  |
| Pacientes con infecciones que requirieron tratamiento con antibióticos (día 90) |                    |                    |                          |                     |                        |                       |                                           |                   |                       |                                                |                                                                                                |             |
| 1                                                                               | ensayos aleatorios | serio <sup>f</sup> | no es serio <sup>c</sup> | no es serio         | serio <sup>b</sup>     | ninguno               | 55/159 (34.6%)                            | 68/159 (42.8%)    | RR 0.81 (0.61 a 1.07) | 81 menos por 1000 (de 167 menos a 30 más )     |  BAJA       | IMPORTANTE  |
| Diagnóstico de diabetes                                                         |                    |                    |                          |                     |                        |                       |                                           |                   |                       |                                                |                                                                                                |             |
| 1                                                                               | ensayos aleatorios | no es serio        | no es serio <sup>c</sup> | no es serio         | muy serio <sup>e</sup> | ninguno               | 6/135 (4.4%)                              | 6/144 (4.2%)      | RR 1.07 (0.35 a 3.23) | 3 más por 1000 (de 27 menos a 93 más )         |  BAJA     | IMPORTANTE  |
| Empeoramiento del control de la diabetes                                        |                    |                    |                          |                     |                        |                       |                                           |                   |                       |                                                |                                                                                                |             |
| 1                                                                               | ensayos aleatorios | no es serio        | no es serio <sup>c</sup> | no es serio         | muy serio <sup>e</sup> | ninguno               | 2/24 (8.3%)                               | 10/15 (66.7%)     | RR 0.13 (0.03 a 0.49) | 580 menos por 1000 (de 647 menos a 340 menos ) |  BAJA     | IMPORTANTE  |
| Chronic Respiratory Disease Questionnaire (CRQ)                                 |                    |                    |                          |                     |                        |                       |                                           |                   |                       |                                                |                                                                                                |             |
| 1                                                                               | ensayos aleatorios | no es serio        | no es serio <sup>c</sup> | no es serio         | serio <sup>g</sup>     | ninguno               | 55                                        | 54                | -                     | MD 0.3 más alto. (0 a 0.6 más alto.)           |  MODERADA | IMPORTANTE  |

CI: Intervalo de confianza RR: Razón de riesgo; MD: Diferencia media

## Explicaciones

- a. Variabilidad significativa en los resultados de los distintos estudios
- b. Numero escaso de eventos; límites del IC95% que apuntan a un efecto beneficioso o perjudicial
- c. Un solo estudio
- d. Desenlace combinado con una importancia relativa muy distinta
- e. Numero muy escaso de eventos
- f. Estudio con un diseño abierto, no se puede descartar la influencia en la valoración de desenlaces subjetivos
- g. El límite superior del IC95% supera el límite establecido como clínicamente relevante (0,5 puntos)

