CONSENSUS DOCUMENT OF THE SPANISH SOCIETY OF INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY (SEIMC) AND THE SPANISH ASSOCIATION OF SURGEONS (AEC) IN ANTIBIOTIC PROPHYLAXIS IN SURGERY

DOCUMENTO DE CONSENSO DE LA SOCIEDAD ESPAÑOLA DE ENFERMEDADES INFECCIOSAS Y MICROBIOLOGÍA CLÍNICA (SEIMC) Y DE LA ASOCIACIÓN ESPAÑOLA DE CIRUJANOS (AEC) EN PROFILAXIS ANTIBIÓTICA EN CIRUGÍA

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CONFLICT OF INTERESTS STATEMENT

The authors declare that they have no conflicts of interest related to this manuscript.

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1. Introduction

Need for the document. Despite advances in knowledge and prevention, surgical site infection (SSI) remains the second leading cause of healthcare-related infection in European countries.[1,2] It is associated with increased health costs, longer hospital stays, rehospitalization, reoperations and increased mortality. Furthermore it has a negative impact on the physical and mental wellbeing of the patient.[3] Prevention of SSIs is achieved by applying a series of interventions in the preoperative, perioperative and postoperative periods, whose effectiveness has been proven. Of these measures, antibiotic prophylaxis has been shown to be the most effective, although its effectiveness is considerably reduced if not accompanied by all the rest.[4]

Prevention of SSIs is one of the priority lines of the WHO aimed at saving lives, reducing costs and avoiding the spread of multidrug-resistant organisms. In November 2016, the WHO published 29 evidence-based recommendations to serve as guidelines that could be applied worldwide. [1,2] Four of these referred to the appropriate use of antimicrobial prophylaxis: 1) Administer the antibiotic before surgery, if it is recommended; 2) administer it within 120 minutes prior to incision (according to the half-life of the drug); 3) do not maintain antibiotics even if drains are still in place; 4) do not maintain prophylaxis after completion of surgery. In 2017, the updated recommendations of the CDC for the prevention of SSI recommended:[5] a) administering antibiotic prophylaxis in surgery only when it is indicated; b) infusing antibiotics before surgical incision in cesarean sections; and c) not maintaining prophylaxis after the wound is closed.[5] Owing to insufficient evidence however, no recommendations could be made for the appropriate time to administer prophylaxis before surgery, dosing for obese patients, or intraoperative redosing.[5]

In spite of the recommendations, and the fact that antibiotic prophylaxis is one of the most effective measures for prevention of SSI, it continues to be administered inappropriately in many hospitals, either because the guidelines are not followed, it is not given at the right time, or is unnecessarily prolonged. [6,7] The European Centre for Disease Prevention and Control (ECDC) recently published a point prevalence survey of antibiotic use, in which prophylaxis in surgery accounted for 24.9% of prescriptions, and more than a half (10,741/19,798, 54.2%) were prescribed for more than 24 hours (country range 19.8–95%, for Spain, above 40%).[8] As will be reiterated throughout this document, failure to administer prophylaxis in accordance with local guidelines or at the appropriate time can increase the risk of SSI. Furthermore, inappropriate administration increases the risk of bacterial resistance and toxicities. This is certainly an important point given that bacterial resistance is currently so serious that is has become a priority objective of health authorities.

At the same time, advances in surgical techniques, the appearance of new ones, the increased number of transplants, and the emergence and expansion of multidrug-resistant pathogens mean that it is essential to revise the antibiotic prophylaxis guidelines used in previous decades.

The last consensus document on surgical prophylaxis was published in 2002 by the EIMC. The *Sociedad Española de Enfermedades Infecciosas* (SEIMC) together with the *Asociación Española de Cirujanos* (AEC) set out to review and update the prevailing recommendations on antimicrobial prophylaxis in surgery and to adapt them to any type of surgery and to current epidemiology. The recommendations made in this guide are based on scientific evidence. Whenever it has not been possible to locate high quality evidence, the editorial committee, together with the coordinators and authors of the guide, have opted to make recommendations based on current knowledge of the etiopathogenesis and risk factors for SSI, pharmacokinetic studies of the antibiotics used in prophylaxis, and clinical experience.

This Consensus Document aims to provide guidelines that will enable the standardized management of AP in elective surgery, as well as the rational, safe and effective use of antibiotics for prevention of surgical site infections.

***Scope of the document*.** This document focuses exclusively on surgical antimicrobial prophylaxis and does not cover other measures that have been shown to be effective in preventing surgical wound infections, such as decolonization of *Staphylococcus aureus* or skin antisepsis. General recommendations are made for antibiotic prophylaxis with specific indications by type of surgery, with grading of recommendations based on scientific evidence. The antimicrobials for different types of surgery are provided with recommended dosages. A few, considered by the committee to be unsuitable for use as prophylaxis, are excluded because of currently high levels of resistance, too broad a spectrum, ecological impact or ability to induce resistance (e.g. quinolones or ertapenem). Recommendations for duration, prophylaxis in special patient populations, and epidemiological settings of multidrug resistance are also provided.

One of the major limitations of this document is that the recommendations cannot always be supported by high-quality evidence due to the design of most studies (the dearth of comparative studies studying the efficacy of antibiotic prophylaxis using placebo or other antimicrobial agents), or low rates of surgical infection for most procedures. On occasions, recommendations are inferred from evidence in other types of surgery in the same anatomical area, or with a similar microbiology. Although the type of antibiotic is recommended, the final choice in each center should be adapted to local epidemiology and local programs aimed at optimizing antimicrobial use. On the other hand, it is not possible to give a general indication in complicated situations, for example, patients undergoing multiple surgeries who have received various antimicrobials, in which case, prophylaxis would need to be individualized according to the risk of infection and the patient's colonization status.

The document is aimed at specialized healthcare professionals involved in surgical procedures, such as anesthetists and surgeons, and those who participate in prevention of surgical infection, such as infectologists, microbiologists, preventivists and pharmacists.

2. Methodology

The two societies, the SEIMC and the AEC, nominated two coordinators for this project: an infectologist (MDT) and a surgeon (JMB). The coordinators, in turn, selected the rest of the panel of experts, which includes surgeons, infectologists, internists and microbiologists belonging to the two societies. The final manuscript was made available to members of both societies for review and suggestions.

This document is, as has been mentioned, an updated revision of the one published in 2002 and is based on recently published, well-designed guidelines that answer questions of clinical interest.

In order to answer each question, a systematic search of the literature was undertaken for relevant studies published between 1970 and October 2018 using the following resources (Cochrane Library), Medline, EMBASE, Scopus, Tryp database, DARE), although a few studies deemed important that were published while the document was being revised have also been included. The studies found were summarized in tabular form following the PICO methodology (table 1), which allowed for a more objective grading of the scientific evidence. The criteria established by the SEIMC for the grading of evidence (table 2) and the evaluation of methodological quality according to the Agree Collaboration (www.agreecollaboration.org) were followed, in accordance with SEIMC regulations. Likewise, the final drafting of the document was carried out in accordance with SEIMC regulations. The final wording of the document was revised in the same way and open to members on the SEIMC web page for review. None of the members of the panel of experts had conflicts of interest to declare for this document.

Table 1. PICO elements of the research question.

Ref	Design	Patient	Surgical Intervention	Comparison	Outcome	Evidence
		Patient group or population of interest?	What is the surgical intervention being conducted?	What, if anything, is the intervention being compared against?	What is the measurable outcome of the surgical intervention?	I II III

Table 2. Table of recommendations.

Strength of recommendation	
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use
Quality of evidence	
I	Evidence from at least one randomized controlled trial supporting the recommendation being made
II	Evidence from at least one well-designed clinical trial without randomization, cohort study or case-controlled study
III	Evidence from expert opinion based on clinical experience or descriptive cases

3. Basic principles of prophylaxis

The general principle of antibiotic prophylaxis is to achieve serum and tissue drug levels above the minimum inhibitory concentration (MIC) needed for the most likely contaminating pathogens in each surgical procedure when the incision is made, and to maintain them throughout the surgical procedure.[5,9] The time taken for an antibiotic to reach effective concentrations in a particular tissue depends on its pharmacokinetic profile and the route of administration used.

3.1. When is prophylaxis indicated?

<u>Search terms</u>: "Antibiotic Prophylaxis" AND "Indications" AND "Recommendations".

The traditional system for evaluating the risk of SSI is based on infection rates for different types of surgery according to whether they are classified as clean, clean-contaminated, contaminated or dirty (*National Research Council*).[10] Antibiotic prophylaxis is indicated when the likelihood of infection is high or when the consequences of postoperative infection in patients are potentially serious (endocarditis, endophthalmitis, prosthetic infection) (**A-III**). Antibiotic prophylaxis is clearly recommended for surgery classified as clean-contaminated and contaminated **(A-II).** In dirty surgery, where there is obvious suppuration or infection, the antibiotic is administered as treatment. In clean surgery, an indication of antibiotic prophylaxis depends on the type of procedure, patient comorbidities and the presence of prosthetic material, although this has not yet been clarified completely.

3.2. Which antimicrobial is most suitable?

<u>Search terms</u>: "Antibiotic Prophylaxis" AND "Surgical Wound Infection/etiology", "Antibiotic Prophylaxis" AND "Practice guidelines as topic".

In clean surgery, the microorganisms involved in SSI are part of the normal skin microbiota (*S. aureus* and coagulase-negative *Staphylococcus*). In clean-contaminated surgery, which includes abdominal surgery and heart, lung and liver transplants, apart from the microorganisms mentioned, gram-negative bacilli and enterococci are also involved, with a variable representation of anaerobes.[11] Table 3 shows the microorganisms involved in SSI by type of surgery in thirteen European countries, according to data in the ECDC-Surveillance Report 2014.[12]

Table 3. Microorganisms detected by type of SSI in 13 countries (2012).[12]

	Coronary by-pass	Cholecystectomy	Colon surgery	Cesarean	Prosthetic hip	Prosthetic Knee	Laminectomy
GPC	60.3	38	31.3	56	66	73.8	68
Enterobacteriaceae	23	45.3	46.6	30.6	17.4	15.2	16
NF-GNB	7.4	4	8.4	3.6	7	4.2	12
Anaerobes	0.5	4.4	6.1	3.9	1.1	1.5	0
Fungal	1.6	2.6	3	0	0.8	0.2	0

As can be seen, the relative contribution of the different groups of microorganisms varies according to the type of surgical operation.

For most surgical procedures, cephalosporins, specifically cefazolin, are the drugs of choice for prophylaxis since they have proven efficacy, an appropriate spectrum of activity against microorganisms commonly found in surgical wound infections, few adverse effects, and are low cost. The clinical trials and meta-analyses proving their efficacy are not recent,[13,14] but are included in most of the guidelines for antibiotic prophylaxis in surgery.[15,16]

Sufficiently strong evidence has not been found to show lower rates of surgical site infection when using broad-spectrum antimicrobials than ones with a narrower spectrum, such as cefazolin.[17]

Three meta-analyses have compared the efficacy of beta-lactams versus glycopeptides (vancomycin or teicoplanin) for antibiotic prophylaxis in surgery. Bolon et al[18] found that the two groups of antibiotics were equally effective for reducing the risk of surgical site infection in cardiac surgery, although beta-lactams reduced the risk of deep sternal wound infection, and glycopeptides were more effective in one subset analysis for preventing SSIs caused by methicillin-resistant *Staphylococci*. Chambers et al[19] found no differences in efficacy between these two groups of antibiotics for reducing the risk of SSI in different types of surgery (cardiac, vascular and trauma surgery) and confirmed that there was a lack of consensus on the hospital prevalence threshold for MRSA when a switch from beta-lactams to glycopeptides would be recommended. Vogt et al[20] for their part, analyzed a subset in two clinical trials on prophylaxis in primary joint arthroplasty without finding differences in efficacy between these two antibiotic groups.

In colorectal surgery, a meta-analysis[21] including 260 clinical trials with 68 different antibiotics, 24 of them cephalosporins, and 43,451 patients, found that covering anaerobes and Enterobacteriaceae with an antibiotic or combination of antibiotics active against both groups of microorganisms was much more effective for reducing the SSI rate than covering anaerobes only or Enterobacteriaceae only.

Recommendations

*The antibiotic must be active against the organisms most frequently isolated in each type of procedure, although the majority of experts advise the use of a first- or second-generation cephalosporin **(A-III)**.*

- ✓ *The choice of antibiotics should take into account local epidemiology and antimicrobial susceptibility patterns of the organisms that cause surgical infections in the hospital **(A-III)**.*
- ✓ *First- and second-generation cephalosporins, fundamentally cefazolin, are the antibiotics of choice for most indications **(A-I)**.*
- ✓ *In cases of allergy to beta-lactams, a history of methicillin-resistant Staphylococcus aureus (MRSA) colonization or infection, or a very high prevalence of SSI caused by MRSA in the hospital, a glycopeptide may be used **(A-I)**.*
- ✓ *In colorectal or gynecological surgery where anaerobic organisms and Enterobacteriaceae are highly likely to be involved in surgical wound colonization, it is recommended to choose an antibiotic or combination of antibiotics with activity against both groups of organisms **(A-I)**.*

3.3. When is the right time to administer antibiotic prophylaxis?

<u>Search terms</u>*: "Antibiotic Prophylaxis" AND "Practice guidelines as topic". "Antibiotic Prophylaxis" AND "Administration and dosage".*

A systematic review and meta-analysis[22] that included 54,552 patients from 13 observational cohort studies[23–35] and one case-control study[36] showed that the risk of SSI doubled when antibiotic prophylaxis was administered after surgical incision (OR 1.89, 95%CI 1.05-3.4) and increased fivefold when it was administered too early, more than 120 minutes before incision (OR 5.26, 95%CI 3.29-8.39) compared to within 120 minutes before the first incision. One clinical trial[29] found no differences in rates of surgical site infection between two groups of patients: one was given antibiotics early (between 30 and 75 minutes before incision) and the other late (between 0-30 minutes before incision). The SSI rates were 4.9% and 5.3% respectively (OR 0.93 95CI% 0.72-1.21). The clinical trial included 5,175 patients undergoing colorectal, vascular and trauma surgery who received 1.5 g of cefuroxime as single doses (plus 500 mg of metronidazole for abdominal surgery). Based on the evidence available therefore it is not possible to specify precisely when prophylaxis should be administered within the 120-minute time interval before incision.

In the case of surgery requiring limb ischemia with tourniquet inflation, such as orthopedic surgery, there is little evidence about the best time to administer prophylaxis. A clinical trial conducted with elective surgery patients for open reduction and internal fixation of fractures (n=106) compared administration of cefuroxime 5 minutes before tourniquet inflation vs. 1 minute after inflation.[37] The rate of SSI was significantly lower in the group that received prophylaxis before ischemia (3.9% vs. 14.8%). In an earlier randomized clinical trial (RCT) of 908 patients undergoing primary knee arthroplasty, 1.5 g of cefuroxime administered 10-30 minutes before ischemia (standard arm) was compared with 1.5 g of cefuroxime before release of the tourniquet (experimental group).[38] The rates of deep tissue infection after one year of follow-up were 3.6% in the standard group and 2.6% in the experimental group, with no significant differences. It is worth noting that in the first group, 12.5% of infections were culture negative vs. none in the experimental group; polymicrobial infections caused by gram-negative bacilli and enterococci were also more common. The may be explained in part as due to the decreased antibiotic levels after ischemia.[39] Pending more robust studies, administration of antibiotics before inflation of the tourniquet continues to be recommended.

Recommendations

Antibiotic prophylaxis in surgery should be administered within 120 minutes prior to incision **(A-I)**.

- ✓ *In the case of beta-lactams with short half-lives (e.g. penicillins and cephalosporins such as cefazolin, cefoxitin and cefuroxime), it is advisable to administer them within 60 minutes prior to incision* **(B-II)**.
- ✓ *In the case of vancomycin, aminoglycosides and fluoroquinolones, intravenous infusion should commence 90 minutes prior to incision, since these antibiotics require long infusion times* **(B-II)**.
- ✓ *In the case of surgery requiring limb ischemia, administer the prophylaxis before inflating the tourniquet* **(A-III)**.

3.4. What is the appropriate dose?

<u>Search terms</u>: *"Antibiotic Prophylaxis" AND "Practice guidelines as topic". "Antibiotic Prophylaxis" AND "Administration and dosage".*

Most experts consider that the dose used in prophylaxis should approach the upper limit of the therapeutic dose (e.g. 2g of cefazolin).

There is some evidence indicating that a starting dose of 1 g of vancomycin (15 mg/kg based on total body weight) may be insufficient as prophylaxis in cardiothoracic surgery, and an initial dose of 20mg/kg of total body weight is recommended.[40]

Tables 4 and 5 show initial doses of antimicrobials, both oral and intravenous, for surgical prophylaxis in adults and children.

Recommendations

- ✓ *It is generally accepted that the antibiotic dose used in prophylaxis is the same as the one used to treat the infection* **(A-III)**.

3.5. Should the dose be modified for the obese patient?

<u>Search terms</u>: *"Antibiotic Prophylaxis" AND "Obesity" OR "Morbid obesity" OR "Overweight" OR "Body Weight". "Antibiotic Prophylaxis" AND "Pharmacokinetics" OR "Pharmacodynamics" combined with terms for types of antibiotics ("Betalactams" OR "Cephalosporins" OR "Aminoglycosides" OR "Fluoroquinolones" OR "Glycopeptides") or individual antibiotics (e.g. "cefazolin").*

The greatest challenge in surgical antibiotic prophylaxis involves selection of the initial dose taking into account body weight. With antimicrobials such as aminoglycosides, renal function is another challenge. With respect to body weight: in the obese patient, there is a risk of underdosing drugs that are lipophilic in nature (such as metronidazole) if dosing is based on ideal body weight, while for drugs that are hydrophilic in nature (such as aminoglycosides), there is a risk of overdosing if the total weight of the patient is used. Pai[41] proposed calculating the initial dose for the obese patient based on the formula:

Dosing for the obese patient = standard dose for average weight x (obese patient weight/average weight) β

where β has a value between 0.5–0.75.

Using this approach, a dose of 750 mg in a patient of average weight (75 kg) increases to an initial dose of 1060–1260 mg in a patient of 150 kg. The dose is increased by 40–70% in patients between 120–180 kg. In the morbidly obese (180–270 kg), the initial dose may be double that of the patient of average weight. This is the basis of the initial dose of 2 g of cefazolin in surgical prophylaxis for patients who weigh <120 kg and of 3 g in patients of >120 kg.

Variability in serum and tissue antibiotic concentrations has been observed in obese patients. This is due to physiological changes that increase the volume of distribution (Vd) and body clearance rate (CL) of the drug, although not necessarily in proportion to total body weight.[42]

The Vd and CL of vancomycin are increased in the obese patient, and various studies have shown that there is a correlation between these parameters and total body weight.[43] Given the variability in serum concentrations observed in obese patients, the initial dose of vancomycin in patients with normal renal function should be at least 20 mg/kg, determined according to total body weight, with an infusion time of 1.5 to 2 hours. The aim of this initial dose is to achieve target trough levels of >10 mg/L as rapidly as possible, which allows for efficient exposure of bacterial isolates with MIC values of ≤1 mg/L. The target pharmacokinetic/pharmacodynamic (PK/PD) index of free drug (50% protein binding) to MIC ratio of *f*Cmin/MIC>4 is attained with this scenario.[44]

To calculate the initial dose, calculate the Vd using the formulas:

Vd = 0.5 L/kg x total weight (kg), for patients with total body mass index (BMI) ≥ 40 kg/m^2.

Vd = 0.7 L/kg x total weight (kg) for patients with BMI between 30-39 kg/m^2.

Once the Vd has been calculated, calculate the initial or loading dose using the formula:

Initial dose = Vd x target peak. The target peak is normally set at between 30-40 mg/L.

According to most experts, to avoid overdosing, the loading dose (e.g. for the obese patient of 150 kg, the initial dose for a peak of 30 mg/L would be 2250 mg) and the maintenance dose should not exceed 3 g and 2 g, respectively.[20]

There are few data on the recommendations for teicoplanin prophylaxis in obese patients. In general, for patients of <85 kg, the recommended dose is the standard one of 800 mg. For patients of 85 kg or more, it is recommended to dose according to body weight (10–12 mg/kg).[45,46]

In the case of aminoglycosides, with variable increases in the Vd and the CL relative to non-obese patients, a generally accepted strategy is to calculate the dose using adjusted weight (ideal body weight plus 40% of the difference between total and ideal body weights).

To calculate ideal body weight (IBW):

IBW in men in kg = 50 + [0.9 x (height in cm – 152)]

IBW in women in kg = 45 + [0.9 x (height in cm – 152)]

To calculate adjusted body weight (ABW) or lean weight:

ABW in kg = IBW + 0.4 x (total weight– IBW)

Since exposure to the drug (as measured by the area under the concentration-time curve (AUC)), reflects the dose administered and systemic clearance rate, it has been recommended that the initial aminoglycoside dose should be based on estimated renal function and predefined efficacy values (AUC over a 24-hour interval, AUC 0-24: 75, 150 and 300 mg·h/L for gentamicin, tobramycin and amikacin, respectively).[47] For example, in an obese patient of 130 kg with CrCl of 75 mL/min (4.5 L/h), gentamicin clearance (CL) is expected to be 4.05 L/h (90% of CrCl). In order to achieve the predefined value of 75 mg·h/L, a single dose of 304 mg (75 mg·h/L x 4.05 L/h) should be administered.

One study demonstrated that levofloxacin clearance in the morbidly obese (body mass index ≥40 kg/m^2) correlates better with estimated CrCl using the Cockcroft-Gault equation based on ideal body weight.[48] In view of this, it is proposed to calculate the initial dose using CrCl based on ideal body weight.[48]

Glomerular filtration rate (mL/min) = [(140 – age in years) x ideal body weight in kg] / (serum creatinine in mg/dL x 72).

Calculating maintenance doses for prolonged prophylaxis in obese patients (during longer surgical procedures, for example) is not well resolved, since drug concentrations are frequently not monitored. For some antibiotics, such as glycopeptides and aminoglycosides, dosages based on estimated renal function may be a reasonable, clinically useful alternative.[49,50]

Recommendations

In obese patients, the concentrations of some antibiotics may be modified due to pharmacokinetic alterations. Pharmacokinetic parameters such as volume of distribution and drug clearance may be greater in obese patients, but frequently not proportional to total body weight **(A-II)**.

- ✓ *Obese patients may require higher starting doses. The conventional dose for non-obese patients can lead to obese patients being underdosed for some drugs. By the same token, dosing based on total bodyweight may lead to overdose in the obese patient* **(A-II)**.
- ✓ *The use of surrogate descriptors of total bodyweight, such as ideal weight or adjusted weight, may correct the problem of overdosing based on total weight in the obese* **(A-II)**.
- ✓ *Calculating maintenance doses for prolonged prophylaxis in the obese (in lengthy surgeries, for example) is not well resolved, although the approach to dose selection based on estimates of renal function may be a reasonable, clinically useful alternative* **(A-II)**.

3.6. Is it necessary to repeat doses during surgery?

Search terms: *"Antibiotic Prophylaxis" AND "Administration and dosage".*

In a retrospective study, Zanetti et al[51] demonstrated that one or two doses of cefazolin (half-life 1.8 hours) were equally effective in cardiac surgery procedures of <240 minutes duration, but that the additional dose in longer procedures of 400 minutes or more reduced the rate of infection by 8% (from 16% without intraoperative redosing to 7.7% with the additional dose, OR 0.44 95%CI 0.23-0.86).

Few studies have determined variations in antibiotic concentrations during surgery and the need for additional intraoperative dosing. Two pharmacokinetic studies in colorectal surgery [52,53] showed that that the need for additional dosing during long surgeries (operations lasting more than 2 hours) was determined by the characteristics of the patient. In patients with moderate and normal kidney function, an additional dose of cefuroxime was required every 4 h and 2 h respectively, until the end of surgery. With metronidazole, an additional dose was needed after 4 hours of surgery in patients with body weights of approximately 90 kg. Additional doses were not needed for subjects of lower weight. Various PK studies of cefazolin in cardiac surgery with cardiopulmonary bypass[54,55] in children and adults with preserved renal function have shown that the standard prophylactic regimen of 2 g in anesthetic induction with a repeat dose after 4 hours is not sufficient to maintain target concentrations of ≥40 mg/L (≥8 mg/L of free drug concentration, in other words, 4 x MIC against most of the sensitive skin microbiota with MICs ≤2 mg/L) for the entire duration of the surgery. The authors proposed alternative regimens (in children, an additional bolus at the start of the cardiopulmonary bypass; in adults, 2g every 3 hours during surgery) for patients with preserved renal function in prolonged surgery.

On the other hand, a study conducted among adults (with cefazolin)[56] and another one (with cloxacillin)[57] showed that significant losses of blood (>1,500 mL) in major surgical procedures were associated with antibiotic concentrations below the therapeutic levels.

Table 4 summarizes the doses and timing of redosing, if applicable, based on the half-life of the antibiotic in pharmacokinetic studies. As can be observed from the table, in the case of cephalosporins, the timing interval for repeat doses has been shortened in patients with preserved renal function, who are the ones at higher risk of underexposure to those antibiotics.

Table 4. Recommended starting doses of the antimicrobials most commonly used via the intravenous route in surgical prophylaxis, and for repeat dose, if applicable. [45,46,52–55,58,59]

Antimicrobial	Recommended doses			Plasma half-life in adults with normal kidney function (h)	Recommended redosing interval (h) of the second dose (with respect to the first) with normal kidney function
	Adults	Children	Infusion time (min)		
Cefazolin	2 g, 3 g for patients of ≥120 Kg	30 mg/Kg	30	1,8	3
Cefuroxime	1,5 g	50 mg/Kg	30	1,4	2
Cefoxitin	2 g	40 mg/Kg	30	1	1
Amoxicillin-clavulanic acid	2.000/200 mg	50/12.4 mg/kg	30	1	3
Azithromycin	500 mg		60 Diluted in 250 mL of physiological serum (concentration of 2 mg/mL)	11-14 (after 1st dose)	24
Clindamycin	900 mg	10 mg/Kg	30	2,5	6
Gentamicin	5 mg/Kg (dosing weight, DW) DW = IBW + 0.4 x (TBW-IBW) IBW: ideal body weight, TBW: total body weight	2.5 mg/Kg (based on dosing weight)	30-60	2	-
Metronidazole	500 mg-1500	15 mg/Kg	30-60	7-8	4 (if weight > 90 kg)
Vancomycin	20 mg/Kg	20 mg/Kg	60 (≤ 1 g)	6-8	-

Table 5. Recommended starting doses of the most commonly used oral antimicrobials in surgical prophylaxis [9,45,46,52–55,59]

Antimicrobial	Recommended Dose		Plasma half-life in adults with normal kidney function (h)
	Adults	Children	
Amoxicillin	1000-2000 mg	13.3 mg/Kg	1
Amoxicillin/ clavulanic acid	875-2000/125 mg		1
Azithromycin	500-1000 mg	10 mg/Kg	11-14 (after 1st dose)
Cefuroxime	750-1000 mg		1-2
Doxycycline	100 mg	1.1-2.2 mg/Kg (> 8 years)	14
Fosfomycin trometamol	3000 mg		6

Recommendations

- ✓ *An additional intraoperative dose is recommended when the procedure is more than two times the half-life of the antibiotic* **(B-II)**.
- ✓ *With cefazolin or other antibiotics with a similar half-life, a second intraoperative dose should be administered at 3 hours* **(B-II)**.
- ✓ *An additional dose is recommended when the half-life of the antibiotic is decreased (burns, very high glomerular filtration rates) or there is significant bleeding (> 1,500 mL in adults or 25 mL/kg in children)* **(B-II)**.

3.7. What is the optimal duration?

Search terms: *“Antibiotic Prophylaxis” AND “Administration and dosage”.*

Various studies[17,60,61] have shown that prolonged antibiotic prophylaxis confers no benefit when compared with single-dose or short-duration prophylaxis.

According to the Norwegian Arthroplasty Register,[62] with follow-ups of up to fourteen years, 24-hr prophylaxis in hip arthroplasty is associated with lower rates of reintervention than single-dose prophylaxis.

A meta-analysis[63] and surgical prophylaxis guidelines published shortly before this document[5] support that a single dose administered preoperatively may be sufficient in primary arthroplasty.

Recommendations

- ✓ *For most surgical procedures, a single dose of antibiotic whose half-life ensures sufficient drug concentrations in serum and tissue for the duration of the surgical intervention will be appropriate* **(A-I)**.

4. What adverse effects are associated with surgical antibiotic prophylaxis?

Search terms: *“Antibiotic Prophylaxis” AND “Adverse effects”*

Administration of antibiotic prophylaxis for the shortest effective period helps reduce the adverse effects of drugs such as allergic reactions to medication (beta-lactams in particular), antibiotic-related diarrhea and/or *Clostridioides difficile* infection, development of antimicrobial resistance and acute kidney injury after major surgery and/or concomitant administration of certain drugs, such as aminoglycosides and glycopeptides.

4.1. What should we do when a patient reports a beta-lactam allergy?

Search terms: *“Antibiotic Prophylaxis/adverse effects” AND “Drug hypersensitivity” AND “Betalactams” OR “beta-lactams”.*

Between 90–99% of patients who report a penicillin allergy, or have a history of vague allergic episodes, are not allergic (i.e. do not present immediate hypersensitivity reactions) and <3% of patients who are allergic to penicillin are cross-reactive with cefazolin.[64] In addition, a retrospective cohort study showed that the risk of SSI was much higher in patients labeled beta-lactam-allergic, possibly because they were given less effective second-line antibiotics as alternatives.[12]

Patients with a history of severe allergic reaction, whether immediately (anaphylaxis, laryngeal edema, bronchospasm, hypotension, urticaria and/or angioedema), within the first hour after administration of a beta-lactam, or delayed (Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome and organ-specific reactions) should not receive beta-lactam prophylaxis when effective therapeutic alternatives are available. There is currently no evidence on how to reduce the risk of anaphylactic shock in patients about to receive antibiotic prophylaxis.[50]

Use of a cephalosporin is not recommended if there is a history of penicillin allergy and there are no skin tests available that can predict cephalosporin allergy.[43]

In cases where the patient has a mild delayed reaction (a maculopapular rash with aminopenicillins, for example), and bearing in mind that cross reactivity between penicillins and cephalosporins is close to 10%, an interventionist approach may be taken. Another beta-lactam (e.g. cephalosporins) may be administered provided that it has a different side chain from the beta-lactam that induced the allergic reaction.[65]

As a general rule, other beta-lactams can be used, provided that they are supported by allergen exposure testing.[13]

Recommendations

- ✓ *Clarifying possible beta-lactam allergy should be a routine part of the pre-anesthesia evaluation and pre-operative care and attention* **(B-II)**.
- ✓ *Patients with a history of severe allergic reaction, whether immediate (occurring within the first hour of beta-lactam administration) or non-immediate, should not receive beta-lactams as prophylaxis when there are other effective therapeutic alternatives* **(B-III)**.
- ✓ *Other beta-lactams may be employed (with a different side chain from the beta-lactam implicated in the allergic reaction), provided that the allergy study has corroborated it through exposure tests* **(B-II)**.
- ✓ *Local AP guidelines should consider alternatives to beta-lactams that are of proven efficacy for those patients who have allergies* **(B-III)**.

4.2. Antibiotic-associated diarrhea and *Clostridioides difficile* infection.

Search terms: *"Antibiotic Prophylaxis/adverse effects" AND "Clostridium difficile" OR "Clostridioides difficile".*

There is no evidence on how to reduce the incidence of antibiotic-associated diarrhea in patients who receive surgical antibiotic prophylaxis.

In an epidemiological study of *C. difficile* infection, surgical antibiotic prophylaxis was the only risk factor found associated with its development. Of 7,600 patients with exposure to prophylactic antibiotics, 1.5% of those who received them as their sole antibiotic treatment developed *C. difficile* infection.[66]

There is evidence that the risk of developing *C. difficile* infection is higher with multiple doses of cephalosporins than with the single-dose regimen. In a study of 1,800 patients undergoing hip fracture surgery, the switch from an antibiotic prophylaxis policy of three doses of cefuroxime (1.5 g) to single-dose cefuroxime (1.5g) with gentamicin (240 g) significantly reduced *C. difficile* infection (from 4.2% to 1.6%).[67] It was also shown that there was an increased risk of *C. difficile* infection in patients who, after discontinuation of antibiotic prophylaxis following surgery for primary arthroplasty, had to be treated with different antibiotics for concomitant infections during admission.[68]

In a retrospective multicenter cohort of 79,058 patients who underwent cardiac, orthopedic, colorectal or vascular surgery, after multivariable logistic regression with adjustments for confounders, the risk of postoperative *C. difficile* infection was associated with duration of prophylaxis (24-<48 hours: OR 1.08 [95%CI 0.89-1.31]; 48-<72 hours: OR 2.43 [95%CI 1.80-3.27;>72 hours: OR 3.65 [95%CI 2.40-5.53),[69] and extended duration did not lead to further reductions in surgical site infection. In the unadjusted analysis, the numbers needed to treat (NTT) to find one *C. difficile* infection at each time interval were 2,000, 50 and 20, respectively.

Recommendations

- ✓ *There is an increased risk of C. difficile infection with some antibiotics used in AP, such as the cephalosporins, carbapenems, fluoroquinolones and clindamycin* **(A-II)**.
- ✓ *There is an increased risk of C. difficile infection if AP is prolonged* **(A-II)**.

4.3. Increased antimicrobial resistance.

Search terms: *"Antibiotic Prophylaxis/adverse effects" AND "antimicrobial resistance".*

There is evidence that short-duration prophylaxis in head and neck surgery has a lower rate of postoperative infection with methicillin-resistant *S. aureus* than long-duration prophylaxis.[70]

In a 4-year observational cohort study, the risk of acquired antimicrobial resistance increased when prophylaxis in cardiovascular surgery lasted for more than 48 hours (adjusted OR 1.6; 95%CI 1.1-2.6).[71]

Recommendations

- ✓ *Use of single doses in surgical prophylaxis, with special exceptions (such as prolonged surgery and significant loss of blood, among others) helps minimize acquired resistance to antimicrobials* **(A-II)**.

4.4. Increased risk of acute kidney injury

<u>Search terms</u>: *"Antibiotic Prophylaxis/adverse effects" AND "Acute Kidney Injury".*

The incidence of acute kidney injury (AKI) in hospitalized patients in acute care hospitals is 5%–7%. Between 30%-40% of these occur in the perioperative period. Morbidity and mortality increase in the postoperative period and it is estimated that up to 30% are iatrogenic and/or potentially preventable.[72]

Using logistic regression, Bell *et al*.[73] found seven independent predictors of AKI in patients undergoing orthopedic surgery: male sex, older age, diabetes, number of prescribed drugs predisposing to renal impairment, lower estimated glomerular filtration rate, use of angiotensin II-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) and higher ASA (American Society of Anesthesiologists) grade. The same group showed that AKI affected up to 11% of patients who had undergone orthopedic surgery, and long-term survival was worse, even in patients with milder forms of kidney injury (stage 1) compared with patients without kidney injury.

In this respect, both the guidelines as well as most of the experts recommend serial measurements of serum and urine creatinine in the preoperative (kidney function tests and grading) and postoperative assessments.[74] If, in addition, these patients have received prophylaxis with aminoglycosides or glycopeptides, the risk of developing AKI increases. This was demonstrated in the United Kingdom when the prophylaxis guidelines in orthopedic surgery changed from cefuroxime to flucloxacillin plus gentamicin to reduce the number of *C. difficile* infections; the percentage of AKI rose from 6.2% to 10.8% in Scotland,[75] and from 1% to 8% in England.[76] Likewise, in an attempt to control MRSA infections in primary hip and knee arthroplasty, and after adding vancomycin to cefazolin, Maxwell Courtney et *al*[77] detected a significant increase in AKI (13% versus 8% in the cefazolin group) which were also of greater severity (AKI stages II and III). In that study, dual prophylaxis (vancomycin and cefazolin), higher ASA grade and kidney disease prior to intervention were independent risk factors for AKI.

In the multicenter cohort mentioned in section 4.2, duration of antibiotic prophylaxis was associated with greater risk of acute kidney injury in cardiac surgery procedures (duration 24-<48 hours: OR 1.03 [95%CI 0.95-1.12]; 48-<72 hours: OR 1.22 [95%CI 1.08-1.39]; >72 hours: OR 1.82 [95%CI 1.54-2.16]) as well as non-cardiac procedures (duration 24-<48 horas: OR 1.31 [95%CI 1.21-1.42]; 48-<72 hours: OR 1.72 [95%CI 1.47-2.01]; >72 hours: OR 1.79 [95%CI 1.27-2.53]) and the NTT in the unadjusted analysis were 9, 4, and 2, respectively.[69]

Recommendations

In the perioperative phase, the procedures in major and trauma surgery may expose the patient to non-specific acute kidney injury, even when there is no previous kidney disease. Furthermore, these patients may receive prophylaxis with antimicrobials such as aminoglycosides or glycopeptides, which are associated with nephrotoxicity **(A-II)**.

- ✓ *In major surgery patients, serial serum and urinary creatinine measurements should be requested in the preoperative assessment as well as ≥ 24h after surgery to check the degree of renal function, paying special attention to patients who have received prophylaxis with aminoglycosides or glycopeptides* **(A-II)**.

4.5. Should prophylaxis be switched in patients colonized with multidrug-resistant organisms (MDROs)?

<u>Search terms</u>: *"Antibiotic Prophylaxis" AND "methicillin-resistant Staphylococcus aureus"; "Antibiotic Prophylaxis" AND "Extended-spectrum Beta-lactamase–producing Enterobacteriaceae"; "Antibiotic Prophylaxis" AND "multidrug-resistant microorganism".*

There is no evidence to show that MDRO carriers have a higher risk of SSI than carriers of susceptible strains.

Methicillin-resistant *Staphylococcus aureus* (MRSA) carriage has been associated with increased risk of SSI, particularly in orthopedic surgery.[78–84] There is less evidence for patients colonized with multidrug-resistant gram-negative bacteria. A prospective study in a cohort of patients who underwent colorectal surgery showed a higher incidence of SSI, and of SSI caused by ESBL-producing Enterobacteriaceae, in patients colonized prior to surgery, than in those not colonized.[85] A retrospective study carried out in children who underwent cardiac surgery[86] found an increased risk of post-sternotomy wound infection in children who were colonized. Nevertheless, in a study carried out in Tanzania, where colonization with ESBL-producing Enterobacteriaceae is highly prevalent, colonized patients were not shown to be at increased risk of infection. [87]

In patients colonized with MRSA, glycopeptide prophylaxis has not been shown to reduce the overall rate of surgical site infection, except in the case of infections caused by resistant staphylococci.[88–90] In some studies, an increase in the overall rate of SSI has been observed.[91] Prophylaxis with glycopeptides plus beta-lactams has been shown to reduce the SSI rates, especially in conjunction with other bundled decolonization and topical decontamination measures in the patient,[90,92] principally in orthopedic and cardiac surgery.

In patients colonized with multidrug-resistant gram-negative bacilli, there is no evidence to support switching prophylaxis. In a retrospective study performed in a hospital with a high prevalence of ESBL-producing Enterobacteriaceae, standard prophylaxis and carbapenem prophylaxis were compared in 266 patients undergoing cardiac surgery, without finding differences in the rates of surgical site infection.[93] In a non-randomized, prospective study published in 2019 in patients colonized with ESBL-producing Enterobacteriaceae undergoing colorectal surgery, prophylaxis with ertapenem reduced the overall incidence of SSI but not the incidence of deep/organ-space surgical site infections.[94]

Recommendations

- ✓ *In high-risk surgery (cardiac, orthopedic) in patients with MRSA colonization, a glycopeptide plus a beta-lactam can be given as prophylaxis, accompanied by other measures for decolonization* **(A-II)**.
- ✓ *For patients with extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae colonization, prophylactic coverage should only be considered in high-risk patients* **(B-III)**.

5. Recommendations by type of surgery

5.1. General comments on clean surgery (excluding cardiac, orthopedic and neurological surgery)

<u>Search terms</u>: *"Antibiotic Prophylaxis" AND "Clean Surgery".*

Table 6 lists various criteria for deciding when antibiotic prophylaxis is not necessary. Generally speaking, prophylaxis is not necessary for clean, non-prosthetic surgery lasting less than two hours, with little tissue attrition, since the risk of infection should be well below 3%. Prophylaxis is indicated for placement of a prosthesis or intravascular implant or when the potential effects of infection are very serious or irreversible (endophthalmitis, infected hernia mesh or vascular access device).

The most commonly used antibiotics are cefazolin, second-generation cephalosporins or amoxicillin-clavulanic acid. For patients with beta-lactam allergies, clindamycin or vancomycin are used.[9]

Table 6. Criteria when antimicrobial prophylaxis may be dispensed with

- *Clean surgery*
- *Duration < 2 hours*
- *No prosthetic material*
- *Age < 65 years*
- *No comorbidities, not obese*
- *No transfusion*
- *No active distant site infection*
- *The SSI would not be potentially serious.*

Modified by Mensa et al. [59]

5.2. Plastic surgery and dermatological surgery

<u>Search terms</u>: *"Antibiotic Prophylaxis" AND "Clean Surgery" OR "Dermatologic surgery".*

Clean surgery covers a comprehensive range of procedures that include plastic, dermatological and reconstructive surgery. These procedures range in scope from primary surgical wound closure, grafts and flaps to tissue transplants. Most of these procedures are associated with an SSI rate of less than 5%, although figures of 5-10% have been reported for oral procedures, such as wedge excision of the lip or ear, flaps on the nose~~,~~ and head and neck flaps. Apart from the known risk factors for any SSI, factors that increase the risk of infection include skin implants, irradiation before the procedure, procedures below the waist.[9] The microorganisms contaminating the surgical wound come from the patient's skin and the operating theatre setting. Those most frequently isolated in SSIs in plastic surgery are *S. aureus*, coagulase-negative staphylococci and streptococci. Gram-negative bacilli are frequently also implicated when macerated or moist areas are involved, in surgery is below the waist, or when the patient has diabetes or is obese.[9]

Antibiotic prophylaxis is a controversial subject in this type of surgery. It may play only a complementary role to the proper preparation of the patient and correct surgical technique, although it has been indicated in various situations.

Most of the placebo-controlled clinical trials and retrospective studies of plastic surgery procedures have not found that antimicrobial prophylaxis significantly reduces the risk of surgical infection, nor in nose and face plastic surgery that does not involve implant placement.[95–100]

A consensus document published by the American Association of Plastic Surgeons based on meta-analyses of published clinical trials concluded that prophylaxis is not necessary in clean plastic surgery procedures without grafts (including abdominoplasty).[95] A single clinical trial of moderate quality supports prophylaxis in abdominoplasty without grafts.[101]

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in clean surgery without implant* **(D-I)**
- *Recommended in case of risk factors (table 6) or presence of implants* **(C-II)**

Antimicrobial: *cefazolin* **(A-II)**

Beta-lactam allergy: *vancomycin/teicoplanin or clindamycin* **(B-II)**

Duration: *single preoperative dose* **(A-II)**

5.3. Hernia surgery and repair

Search terms: *"Antibiotic prophylaxis" AND "Hernia repair" OR "Hernia mesh repair" OR "Herniorrhaphy" OR "Hernioplasty".*

There is some controversy surrounding prophylaxis in hernia surgery because of the contradictory findings in various meta-analyses.

Since 2007, a number of meta-analyses have found that prophylaxis showed a protective effect in open hernioplasty.[102–104,105] In 2016, another meta-analysis[106] advised against routine prophylaxis, although it is indicated if there are risk factors such as recurrence, advanced age, immunosuppression, drainage or if surgery is expected to be prolonged. A 2017 meta-analysis[107] showed that a single preoperative dose of cefazolin and beta-lactam/beta-lactamase inhibitors was superior to placebo, but not to cefuroxime and fluoroquinolones, and that there were no differences between the antimicrobials used.

With respect to laparoscopic hernia repair, various studies have reported significantly lower rates of SSI.[108,109] In incisional hernia or eventration, there are also lower rates using laparoscopy.[110] The European Association for Endoscopic Surgery (EAES)[111] considers that there is no evidence for routine use of prophylaxis in laparoscopic hernioplasty, and the European Hernia Society (EHS) considers that, in this case, the NNT tend to infinity. [112]

Based on the evidence available and given the difficulty of predicting some of the risk factors in the preoperative period, prophylaxis is recommended in herniorraphy and open inguinal hernia repair, and in other types of abdominal hernioplasty (inferred from evidence in inguinal surgery).

A single dose of a first-generation cephalosporin is recommended. For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin (see section 4.5). For patients with beta-lactam allergies, alternatives include clindamycin and vancomycin.

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended in open inguinal herniorrhaphy and hernioplasty* **(B-I)**
- *Recommended in the rest of the open abdominal hernioplasties (by inference from the evidence in inguinal hernia)* **(B-II)**
- *Not recommended in laparoscopic inguinal hernioplasty* **(D-I)**

Antimicrobial: *cefazolin* **(A-I)** *+ vancomycin in case of MRSA colonization* **(B-III)**

Beta-lactam allergy: *vancomycin/teicoplanin or clindamycin* **(B-II)**

Duration: *single preoperative dose* **(A-I)**

5.4. Breast surgery and breast cancer surgery

Search terms: *"Antibiotic prophylaxis" AND "Breast surgery" OR "Breast cancer surgery" OR "Breast reduction surgery".*

In both cases, the organisms responsible for SSI are *S. aureus*, other staphylococci and streptococci. *P. aeruginosa, Serratia marcescens* and *Enterobacteriaceae (E. coli, Klebsiella spp, P. mirabilis)* may be found in diabetic and obese patients with maceration on skin folds or in the axilla. The SSI rate in breast implants for aesthetic reasons and after breast reconstruction due to malignancy is between 2%-2.5%, and risk factors have been identified as one-stage breast reconstruction, chemotherapy and neoadjuvant radiotherapy and preoperative biopsy before surgery.[113]

Antibiotic prophylaxis significantly reduces the incidence of surgical site infection in breast cancer surgery without reconstruction (RR 0.67, 95%CI 0.53-0.85).[114] Prophylaxis has also been shown to be effective in patients undergoing immediate reconstruction, who are at greater risk of infection,[113] as well as in breast reduction surgery[115] and breast implants for cosmetic purposes.[116] The antibiotics used are single-dose cefazolin or amoxicillin-clavulanic acid, with clindamycin or vancomycin as an alternative for those with beta-lactam allergy. For allergic patients undergoing surgery below the navel, consider adding gentamicin to cover Enterobacteriaceae.

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended in breast cancer surgery in case of risk factors or neoadjuvant* **(A-II)**
- *Recommended in cancer reconstructive surgery* **(A-I)**
- *Recommended in aesthetic surgery (augmentation, reduction)* **(B-II)**

Antimicrobial: *cefazolin* **(A-I)**

Beta-lactam allergy: *clindamycin or vancomycin* **(B-II)**

Duration: *single preoperative dose* **(A-I)**

5.5. Cardiac and vascular surgery

5.5.1. Coronary artery bypass and valve replacement surgery

Search terms: *"Antibiotic prophylaxis" AND "Cardiothoracic surgery" OR "Cardiac surgery" OR "Nonvalvular cardiovascular surgery".*

Surgical site infection, including mediastinitis and sternal wound infection, are serious complications that occur infrequently after aortocoronary bypass surgery or valve replacement surgery.[117] A number of studies have demonstrated that antibiotic prophylaxis in these procedures is effective for reducing the associated infection rate.[14]

Various risk factors have been associated with infectious complications following cardiac procedures, the most consistent of which are: diabetes, hyperglycemia, peripheral vascular disease, chronic obstructive pulmonary disease, obesity, heart failure, advanced age, need for reintervention, prolonged duration of the procedure, and *S. aureus* nasal colonization. Almost two thirds of the organisms causing postoperative infection in this setting are gram-positive cocci, including *S. aureus*, coagulase-negative staphylococci and more rarely, *Cutibacterium* (*Propionibacterium) acnes*. Prophylaxis should therefore be aimed at providing coverage against these pathogens. Multidrug-resistant gram-positive organisms and gram-negative organisms (Enterobacteriaceae, *Pseudomonas* spp, and *Acinetobacter* spp.) are less frequently involved. Generally, patients with multidrug-resistant colonization or previous infections should receive individualized antibiotic prophylaxis (see point 4.5, prophylaxis in patients with colonization).

First- and second-generation cephalosporins have been the most widely used antibiotics. A meta-analysis comparing prophylaxis using cephalosporins and glycopeptides showed increased gram-positive infections in patients treated with glycopeptides, although fewer infections caused by multidrug-resistant organisms were diagnosed in this group.[18] There is no evidence that clearly supports the use of glycopeptide prophylaxis in centers with a high prevalence of MRSA. Prophylaxis using glycopeptides plus beta-lactams has been shown to reduce the rate of SSI in patients with MRSA colonization when accompanied by topical decolonization.[90,92] An alternative for patients unable to tolerate beta-lactams would be vancomycin or clindamycin. [118] Adding an aminoglycoside may be reasonable in cases where extended-spectrum prophylaxis is required to provide coverage against gram-negative bacteria.[16]

The optimal duration of prophylaxis is not well established. The recommendations vary between a single dose or prophylaxis for up to 24 hours. It was suggested in one meta-analysis that the efficacy of prophylaxis may be greater if it is extended for at least 24 hours after the procedure,[119] although the result were not conclusive owing to heterogeneity of the antibiotic regimens used. What seems to be clear is that prophylaxis should be extended for at least the duration of the procedure.[120] A study has shown that, in order to maintain cefazolin concentrations throughout the procedure in a patient with normal kidney function, it is necessary to administer cefazolin at least every 3 hours during surgery.[55] Another study demonstrated, that in the pediatric population, an additional dose of cefazolin is necessary after starting surgery in order to maintain adequate serum levels of antibiotic.[54]

The practice of continuing prophylaxis until all wound drains and catheters have been removed is not recommended in order to prevent selection of multidrug-resistant organisms, superinfections and drug toxicity.

There is no evidence on prophylaxis in percutaneous coronary interventions such as cardiac catheterization or angiography. In general, it is strongly recommended to maintain full asepsis during artery access.[121]

Nor is there evidence available about antibiotic prophylaxis before transcatheter aortic valve implantation (TAVI). This is a recent technique and the incidence of infection is not very high. In most cases infection seems to be related to bacteremia originating elsewhere, not to the procedure itself.[122,123] Nevertheless, given the morbidity and mortality associated with infectious complications, it is reasonable to administer a pre-operative dose of antibiotic and it is in fact recommended in the guidelines.[124] Cefazolin has been recommended, and vancomycin in those with beta-lactam allergies, although some authors advocate the use of amoxicillin/clavulanic acid for coverage against *E. faecalis*, especially when femoral access is used.[125]

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in percutaneous procedures* **(D-II)**.
- *Recommended in aortocoronary bypass and valve replacement* **(A-I)** *and in percutaneous transcatheter aortic valve implantation* **(B-III)**.

Antimicrobial: *cefazolin or cefuroxime* **(A-I)**

Beta-lactam allergy: *vancomycin* **(A-II)**

Duration: *single preoperative dose* **(A-I)**.

If cephalosporins are used, redose 1 g every 3 hours during the procedure, do not continue after closure **(A-II)**.

5.5.2. Pacemaker and defibrillator insertion

<u>Search terms</u>*: "Antibiotic prophylaxis" AND "Pacemaker" AND "Cardioverter defibrillator".*

The rate of infection associated with pacemaker insertion is around 0.44%.[117] A number of risk factors have been identified, especially, fever within 24 hours before insertion, corticosteroid use for more than one month in the preceding year, and early reintervention due to postoperative hematoma or lead replacement.[120,126,127] A number of studies and a meta-analysis have shown the effectiveness of antibiotic prophylaxis.[128] The AHA guidelines recommend administration of a single dose of antimicrobial before the procedure.[129]

There is limited quality evidence about antibiotic prophylaxis before ventricular assist device (VAD) implantation.[130] Use of prophylaxis is inferred from cardiac surgery and pacemaker insertion. A retrospective study showed no greater risk of infection in patients treated with a single dose than in those treated with several doses of antibiotics.[131]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in pacemaker and defibrillator insertion* **(A-I)**

Antimicrobial: *cefazolin or cefuroxime* **(A-I)**

Beta-lactam allergy: *vancomycin* **(A-II)**

Duration: *single preoperative dose* **(A-I)**

5.5.3. Insertion of central vascular access catheter.

Search terms: "Antibiotic prophylaxis" AND "Catheter-related" OR "Indwelling catheter" OR "Central venous catheter intravascular catheter" OR "Long-term catheter".

In a randomized clinical trial that included 88 patients with hematological malignancies, an association was found between teicoplanin prophylaxis given before insertion of a tunneled central venous catheter and reductions in insertion-site infections, tunnel infection and catheter-related gram-positive septicemia.[132] In another study that included 55 non-cancer patients, antibiotic prophylaxis before insertion of a vascular access device did not lead to a reduction in the rate of catheter-related sepsis.[133] Prophylactic teicoplanin in a randomized clinical trial with 65 patients with hematological malignancies did not reduce the rates of catheter-related infection.[134] In another randomized clinical trial including 98 patients, vancomycin prophylaxis did not reduce the rates of sepsis.[135]

A meta-analysis, first published in 2013 and updated in 2015, which included 11 RCTs and 828 patients, analyzed the efficacy of administering antibiotic prophylaxis before insertion or use of a central venous catheter for the prevention of catheter-related gram-positive infections.[136] Five trials in the meta-analysis[136] found no differences in rates of catheter-related sepsis between a group of patients who received systemic vancomycin, teicoplanin or ceftazidime before insertion and another that did not receive prophylaxis. Six of the studies showed that locking long-term CVCs with a combined antibiotic (vancomycin, amikacin or taurolidine) and heparin solution significantly reduced the rate of catheter-related sepsis compared with a heparin-only solution. For a baseline infection rate of 15%, the authors calculated that the reduction translated into an NNT of 12 to prevent one catheter-related infection. The study concluded that, based on the evidence, this measure would only be justified for high-risk patients or in units where the rate of infection was above 15%. Another study evaluated a 70% ethanol lock prophylaxis as part of a prevention bundle involving children with intestinal failure, showing a significant reduction in catheter-related bloodstream infection rates.[137] In that study, it was difficult to evaluate the role of the lock, since it formed part of a bundle of preventive measures.

In the case of tunneled catheters, colonization and subsequent infection is often the result of catheter colonization due to frequent manipulation of connectors.[138] On the other hand, glycopeptide prophylaxis has been linked to the emergence of resistant organisms, which is why its use is discouraged in many guidelines.[139]

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in implantation of central vascular access catheters* **(D-I)**.
- *An antibiotic lock is not routinely recommended before inserting or manipulating an intravascular catheter* **(D-I)**.

5.5.4. Peripheral vascular surgery (percutaneous and open)

Search terms: "Antibiotic prophylaxis" AND "Peripheral arterial surgery" OR "Vascular surgery".

Infections following peripheral vascular procedures are rare, although if they occur they pose a significant health concern, since they are associated with high morbidity and mortality.[140] Hence, antibiotic prophylaxis is recommended in procedures involving placement of prosthetic material, or high-risk procedures such as aneurysm repair, thromboendarterectomy or venous bypasses.[141]

The main organisms involved in the infections associated with these procedures include *S. aureus,* coagulase-negative staphylococci, and enteric gram-negative bacilli. A number of studies have evaluated the role of MRSA colonization in patients undergoing vascular procedures.[142] Independent risk factors associated with MRSA infection are previous colonization with MRSA, abdominal aortic aneurysm repair and lower limb bypass.[143]

Patients undergoing brachycephalic procedures (carotid endarterectomy, brachial artery repair) without implantation of prosthetic devices do not appear to benefit from antibiotic prophylaxis.[144] There are no well-designed studies for peripheral vascular procedures, so that if prophylaxis is desirable due to risk factors in the patient,[145] it is recommended to follow the approach used in cardiac surgery. Risk factors associated with the placement of vascular stents include duration of surgery (more than two hours), reoperations at the same placement site, stent placement in the lower limbs, presence of hematomas, patients with other intravascular devices and immunosuppressed patients.[146] A meta-analysis of patients who underwent peripheral arterial reconstruction with biologic or prosthetic grafts found that preoperative prophylaxis reduced the risk of wound infection (RR 0.25; 95%CI: 0.17–0.38; p ≤0.001).[147]

Patients undergoing vascular access placement procedures for hemodialysis may benefit from specific anti-staphylococcal prophylaxis. In one study it was demonstrated that the rate of postoperative infection after arteriovenous fistula creation in the upper extremity was lower in the control group (prophylaxis with vancomycin) than in the placebo (1% versus 6%, p= 0.006).[141]

Cefazolin is the preferred antimicrobial agent in most of the studies, because it is the most cost-effective drug. In one study, no differences were found between cefazolin and cefuroxime in patients undergoing lower extremity vascular procedures.[148] Other studies have found no differences between ceftriaxone and cefazolin, or between oral ciprofloxacin and intravenous cefuroxime. There are limited data on the choice of prophylaxis for patients allergic to beta-lactams, although the most commonly used agents have been vancomycin and clindamycin. If coverage against gram-negative organisms is required (if the procedure involves the abdominal aorta or an incision in the groin area), an aminoglycoside can be added to the prophylactic regimen.

With respect to duration, in a meta-analysis of three RCTs, prolonged antibiotic prophylaxis beyond 24 hours after the procedure showed no extra benefit (RR 1.28; 95% CI: 0.82–1.98).[147] In other studies, there was no extra benefit when prophylaxis with cefuroxime was given for 3 days,[149] nor amoxicillin-clavulanic acid for 5 days.[150] In general, all the studies recommend a single prophylactic dose or a maximum duration of 24 h for vascular procedures where prophylaxis is given, regardless of the presence of drains.

Recommendations for antimicrobial prophylaxis

Indication:

Recommended in high-risk vascular procedures, including those in which some type of prosthetic material is to be implanted **(A-I)**.

Antimicrobial: *cefazolin* **(A-I)**. *Adding a second antibiotic with activity against gram-negative bacillus (gentamicin) is suggested if there is risk of exposure to intestinal microbiota* **(B-III)**.

Beta-lactam allergy: *vancomycin* **(B-II)** *or clindamycin* **(C-III)**.

Duration: *single preoperative dose* **(A-I)**

5.6. Ophthalmic surgery

Search terms: *"Antibiotic prophylaxis" AND "Ophthalmic surgery" OR "Intraocular surgery" OR "Cataract surgery" OR "Lacrimal surgery" OR "Post-traumatic endophthalmitis" OR "Post-traumatic open globe-injury".*

Ophthalmic procedures include cataract extraction, vitrectomy, keratoplasty, intraocular lens implantation, glaucoma procedures, strabotomy, retinal detachment surgery, laser-assisted in situ keratomileusis and laser-assisted subepithelial keratectomy. Most of the available data on antimicrobial prophylaxis apply to cataract procedures.

The main objective of antimicrobial prophylaxis is to reduce acute postoperative endophthalmitis. There are limited data concerning the efficacy of antibiotic prophylaxis in the prevention of endophthalmitis and the low rate of postoperative endophthalmitis makes it difficult to find an adequately powered sample size to demonstrate such efficacy. Accordingly, indirect markers of bacterial eradication of normal flora and reduction of bacterial count in the conjunctiva, upper and lower edges of the eyelids, eyelashes and inner canthus are used, preoperatively and postoperatively.[9]

The microorganisms most commonly involved in postoperative endophthalmitis after cataract surgery are coagulase-negative staphylococci (between 25–60%), primarily *S. epidermis*. Other gram-positive organisms identified include *S. aureus*, *Streptococcus* spp., *Enterococcus* spp., *C. acnes* and *Corynebacterium* spp. Gram-negative organisms isolated include species of *Serratia, Klebsiella* spp., *Proteus mirabilis* and *Pseudomonas aeruginosa*. These organisms represent the normal flora most frequently isolated preoperatively.[151,152]

Preoperative antisepsis with povidone iodine is a universally recommended measure and there is strong evidence and a high level of recommendation for intracameral antibiotics to be administered once cataract surgery has been completed to minimize the risk of infection. Most studies used cefuroxime or cefazolin, although based on the evidence available, specific recommendations cannot be made for choice of antimicrobial agent or duration of prophylaxis. As a general principle, the antibiotics used must provide coverage against the organisms that most frequently cause eye infections, such as staphylococci and gram-negative bacteria, in particular, *Pseudomonas* spp. [9,152–163] There is rather less evidence of these antibiotic prophylaxis measures in glaucoma/corneal graft surgery and penetrating eye injury.[164,165]

In penetrating eye injuries, endophthalmitis occurs in up to 13% of cases, most frequently caused by species of staphylococci and *Bacillus cereus* (the latter in as much as 25%). The risk of endophthalmitis is associated with presence of an intraocular foreign body, rural setting of the injury, disruption of the crystalline lens, and delay in primary wound closure.[166] A systematic review and meta-analysis of 3 clinical control trials with low risk of bias[167] and a retrospective study[168] showed that intravitreal antibiotic injections are useful for preventing endophthalmitis, together with systemic prophylaxis with vancomycin and ceftazidime. Nevertheless, the diffusion of antibiotics from plasma to vitreous cavity is not high and sufficient concentrations are not reached to treat or prevent infection, especially with hydrophilic antibiotics such as aminoglycosides, glycopeptides and beta-lactams; linezolid and levofloxacin do however attain sufficient concentrations.[169] In short, in cases with dirty penetrating wounds and risk factors for endophthalmitis, intravitreal and intravenous antibiotic treatment would be indicated, taking into account the diffusion of these into the aqueous humor, and in the rest, surgical prophylaxis would be sufficient.

The evidence for antibiotic prophylaxis in lacrimal surgery is less solid.

Recommendations for antimicrobial prophylaxis in cataract surgery

Indication: *Intracameral administration is recommended immediately after cataract removal* **(A-I)**

Antimicrobial: *intracameral cefuroxime or cefazolin* **(A-I)**.

Beta-lactam allergy: *intracameral vancomycin or moxifloxacin* **(A-III)**

Duration: *single dose* **(A-I)**

Recommendations for antimicrobial prophylaxis in glaucoma surgery and corneal graft

Indication: *Intracameral administration is recommended by inference from cataract surgery* **(A-II)**

Antimicrobial: *intracameral cefuroxime* **(A-I)**.

Beta-lactam allergy: *intracameral vancomycin or moxifloxacin* **(B-III)**

Duration: *single dose* **(A-I)**

Recommendations for antimicrobial prophylaxis in penetrating eye trauma

Indication: *Intravitreal injection is recommended* **(A-I)**

Antimicrobial: *gentamicin + clindamycin* **(A-II)** *or gentamicin + vancomycin* ***(A-III)***

Duration: *single preoperative dose* **(A-I)**

Recommendations for antimicrobial prophylaxis in lacrimal surgery

Indication: *Recommended* **(A-III)**

Antimicrobial: *cefazolin or cefuroxime* **(A-III)**

Beta-lactam allergy: *vancomycin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.7. Neurosurgery

Search terms: *"Antibiotic prophylaxis" AND "Neurosurgery" OR "Craniotomy" OR "Cerebrospinal fluid-shunt surgery" OR "External ventricular drains" OR "Intracranial pressure monitors" OR "Transsphenoidal surgery".*

Neurosurgical procedures include clean surgery (craniotomy, shunt placement for external ventricular drainage of cerebrospinal fluid (CSF) and intracranial pressure sensors) and clean-contaminated (transsphenoidal and pharyngeal surgery). Spinal surgery is dealt with under orthopedic procedures.

The pathogens most commonly involved in SSIs in most of the studies are gram-positives, *S. aureus* and CoNS, some with high rates of resistance to methicillin.[9] *C. acnes* may also be involved in CSF shunt infection and craniotomies. Gram-negative bacteria may also be involved in 5–8% of cases, sometimes in polymicrobial infections.[9]

5.7.1. Craniotomy

Several meta-analyses have demonstrated that antibiotic prophylaxis reduces the rate of post-craniotomy infection at the surgical site and the risk of meningitis.[170,170,171]

There is no agreement about what type of prophylaxis to use, since different antibiotic regimens have been evaluated in various studies and proven to be effective in single dose or multiple dose (such as cefazolin, cefotiam, cefuroxime, cloxacillin, amoxicillin-clavulanic acid, third-generation cephalosporins, trimethroprim-sulfamethoxazole).[172–175] In a meta-analysis, no significant differences were found in the rate of post-craniotomy meningitis between various antibiotic regimens, or in the duration of prophylaxis.[171]

First- and second-generation cephalosporins seem to be a good option. In the meta-analysis by *Liu et al*, third-generation cephalosporins failed to show superiority over conventional antibiotics with respect to either incisional or organ-related infections after neurosurgical procedures.[176]

A recently published meta-analysis concluded that lincosamides, glycopeptides, third generation cephalosporins and penicillin derivatives provide better coverage against SSIs in this type of surgery than do first-generation cephalosporins. However, the meta-analysis only included one controlled clinical trial and six case series (some from 1974) and the results of the latter are from high-risk patients and not therefore extrapolable.[177]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in craniotomy* **(A-I)**

Antimicrobial: *cefazolin* **(A-I)**

Beta-lactam allergy: *vancomycin or clindamycin* **(A-II)**

Duration: *single preoperative dose* **(A-I)**

5.7.2. Placement of ventriculoperitoneal or ventriculoauricular shunt (VPS and VAS) and external ventricular drainage (EVD)

Infections are one of the main complications of a CSF shunt, with a variable rate of between 5% and 10% reported, although they can reach up to 40%. A number of meta-analyses have found a statistically significant decrease in CSF VPS and VAS infection when antibiotic prophylaxis is used. [178–180]

The effect of prophylaxis may be related to the baseline infection rate and is not useful when this is very low (<5%).[179]

Vancomycin prophylaxis reduces the rate of VPS and VAS infections in centers and/or services with high prevalence of MRSA infection.[181]

The usefulness of antibiotic prophylaxis in patients with external ventricular drains has been debated. In an international survey of different EVD specialists, it was recommended by the majority of neurosurgeons (73.5%) versus 59% of intensivists and 35% of infectologists. In a recent systematic review, antibiotic prophylaxis in EVD was observed to reduce the risk of infection (RR: 0.45 (95% CI, 0.27-0.74, p=0.02).[182]

Continuous antibiotic prophylaxis in EVD shows no benefits over perioperative prophylaxis. Hence, discontinuation reduces costs and prevents the appearance of drug-resistant bacteria.[183]

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended in ventriculo-peritoneal or ventriculo-auricular shunt* **(A-I)**
- *Recommended in external ventricular drainage* **(B-I)**

Antimicrobial: *cefazolin* **(A-I)**. *In context of high prevalence of MRSA: vancomycin* **(A-I)**

Beta-lactam allergy: *vancomycin* **(A-II)**

Duration: *single preoperative dose* **(A-I)**

5.7.3. Placement of intracranial pressure sensors (ICP)

The risk factors associated with infection of intracranial pressure monitoring devices are duration of monitoring > 5 days, the presence of ventriculostomy, CSF leak, concomitant infection, replacement of ICP monitor. Nevertheless, based on retrospective cohort studies, use of antimicrobial prophylaxis does not seem to reduce the rate of infection.[184–187]

There are no randomized controlled trials that allow us to demonstrate its usefulness.[184–189]

> ***Recommendations for antimicrobial prophylaxis***
> ***Indication:*** *Not recommended in intracranial pressure sensor placement* **(D-II)**

5.7.4. Transsphenoidal or pharyngeal surgery

There are various retrospective studies of case series in transsphenoidal surgery that analyze different antibiotic prophylaxis regimens with very low rates of infection. [190–194]

In a randomized double-blind controlled study comparing 2 antibiotic prophylaxis regimens (ceftizoxime vs vancomycin and gentamicin) in neurosurgical procedures, it was noted in a subgroup analysis of 129 patients who underwent transsphenoidal surgery that the infection rate was very low.[195]

The use of ultra-short perioperative prophylaxis for the prevention of meningitis after transsphenoidal surgery seems to be efficacious, safe and cheap.[193,194] There are no well-designed randomized controlled studies.

A number of different regimens have been used for antibiotic treatment (cefazolin, cefuroxime, amoxicillin-clavulanic acid, vancomycin plus gentamicin, clindamycin, ceftazidime plus amikacin), but in the absence of comparative studies, no firm recommendations can be made. Taking into account the normal microbial flora of the oropharynx and the etiology of infections described for this type of surgery (enterobacteria, *H. influenzae*, *S. pneumoniae* and other streptococci, *S. epidermidis*),[196] amoxicillin-clavulanic acid could be used as prophylaxis, with clindamycin or vancomycin combined with an aminoglycoside in cases of allergy.[190–195]

> ***Recommendations for antimicrobial prophylaxis***
> ***Indication:*** *Recommended in transsphenoidal or pharyngeal surgery* **(A-III)**.
> ***Antimicrobial:*** *amoxicillin-clavulanic acid* **(A-III)**.
> ***Beta-lactam allergy:*** *clindamycin or vancomycin associate with an aminoglycoside* **(B-III)**
> ***Duration:*** *single preoperative dose* **(A-I)**.

5.8. Head and neck surgery

Search terms: *"Antibiotic prophylaxis" AND "Neck and head surgery".*

5.8.1. Clean surgery: Salivary gland surgery, thyroid surgery, parathyroid surgery, lymphadenectomy, not requiring incision of the pharyngeal/laryngeal mucosa.

Search terms: *"Thyroid surgery" OR "Parathyroid surgery" OR "Clean neck dissections" OR "Head and neck oncological (OR cancer) surgery".*

Systemic administration of prophylactic antibiotics has not been shown to reduce the rates of SSI in patients undergoing clean head and neck surgery.[197–199] A randomized, double-blind, multicenter study of 500 patients who underwent thyroid surgery for multinodular goiter or thyroid carcinoma found no differences in the rates of infection between the control and antimicrobial prophylaxis groups (0.8% vs. 0.4%),[198] and routine use of antibiotic prophylaxis was not recommended for thyroid surgery. In another controlled study[199] including more than 2,000 patients, infection rates were compared in patients with clean thyroid surgery who received piperacillin or cefazolin; no statistically significant differences in SSI rates were found (0.09% vs. 0.28%; p=0.371). A recent systematic review of the literature[200] highlighted very low rates of SSI in transcervical thyroidectomy and minimally invasive techniques, with antibiotic prophylaxis being reserved for cases requiring a transoral approach, where the risk of infection increases slightly because it is "clean-contaminated" surgery. For patients undergoing the latter approach, the recommended antibiotic of choice would probably be amoxicillin-clavulanic acid.

In the review by Simo,[201] low rates of surgical infection were also observed in other procedures such as parotidectomy and submandibular gland resection without antibiotic prophylaxis, and the same level of recommendation could therefore be applied to the other clean neck surgeries in patients whose risk of surgical infection is not very high.

When this type of surgery is accompanied by cervical lymph node dissection, the extensive exposure of tissue may increase the risk of infection. The results of studies comparing the use or non-use of antibiotic prophylaxis in this kind of surgery are not in agreement. In a prospective study, Seven et al[202] found a significant reduction in wound infections in patients undergoing clean neck dissection after introducing antibiotic prophylaxis with cefazolin (1.7% vs. 13.3%; p = 0.02). Two other retrospective studies with a large number of patients observed something similar.[197,203] Nevertheless, a more recent retrospective study conducted with 244 patients undergoing 273 uncontaminated neck dissections found a rate of SSI of 3.3% in the group that received antibiotics versus 0% in the group that did not receive them.[204] The SSI was independently associated with duration of surgery and radical or extended neck dissections. Given the absence of controlled trials, prophylaxis can be considered in patients with extended neck dissections.[197,202,203] Two retrospective studies[204,205] and a clinical trial[206] showed no benefits for duration of prophylaxis ≤24h vs. ≤7 days, but there are no comparative studies of single dose vs. 24 hours.

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in clean head and neck surgery* **(D-I)**.
- *Recommended in extended lymphadenectomies or cervical surgery with multivisceral resection* **(B-II)**.

Antimicrobial: *cefazolin* **(B-II)**

Beta-lactam allergy: *clindamycin or vancomycin* **(B-III)**

Duration: *≤24 hours* **(A-II).** *Possibly a single dose is enough* **(A-III)**.

5.8.2. Clean-contaminated surgery: tonsillectomy, adenoidectomy, laryngectomy tracheotomy and any other surgery involving incision of the pharyngeal-laryngeal mucosa.

Search terms: "Tonsillectomy" OR "Pharyngolaryngeal surgery".

Most of the available guidelines and reviews of clean-contaminated head and neck surgery recommend giving antibiotic prophylaxis in most procedures,[201] although there appears to be no benefit In patients undergoing tonsillectomy. Controlled studies[207–209] have noticed no significant differences in post-operative complications in tonsillectomy patients. Systematic reviews of the impact of prophylaxis in these surgeries have not recommended routine administration of antibiotic prophylaxis either.[210,211]

In patients requiring head and neck cancer surgery for tumors, a very high rate of surgical site infection has been observed, so that antibiotic prophylaxis is recommended.[201] Several controlled studies of small series taking different antibiotic approaches, including cefazolin, ampicillin and third-generation cephalosporins, noted a statistically significant reduction in surgical infection following the administration of antibiotic prophylaxis.[212] It is recommended that prophylaxis duration in clean-contaminated head and neck surgery should not exceed 24 hours.[213] Maintaining antibiotic prophylaxis for more than 24 hours did not significantly reduce the infection rate in patients undergoing myocutaneous flap microsurgery either,[214] so that the recommendation is to maintain prophylaxis for a maximum of 24 hours. In these patients, prophylaxis with clindamycin was associated with higher rates of SSI, [214,215] as were antibiotic approaches not active against gram-negative organisms.[216]

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended in clean-contaminated head and neck surgery* **(A-II)**, *except tonsillectomy and adenoidectomy* **(D-I)**.
- *Recommended in head and neck cancer surgery* **(A-II)**.

Antimicrobial: *amoxicillin-clavulanic acid* **(A-III)**

Beta-lactam allergy: *clindamycin plus gentamicin* **(B-III)**

Duration: *≤24 hours* **(A-II)**. *Possibly a single dose is enough* **(A-III)**.

5.8.3. Sinus and middle ear surgery

<u>Search terms</u>: "Antibiotic prophylaxis" AND "Endoscopic sinus surgery" OR "Clean and clean-contaminated otologic procedures" OR "Cochlear Implantation".

Endoscopic sinus surgery

A meta-analysis evaluated four controlled studies on antibiotic prophylaxis in endoscopic sinus surgery,[217] without finding a significant reduction in the incidence of postoperative infection (RR 0.76 ; 95%CI: 0.64-0.09). Routine use of prophylaxis in endoscopic sinus surgery is not therefore recommended.

Otologic surgery.

In a recent review of the literature on the usefulness of antibiotic prophylaxis in a number of otorhinolaryngology procedures,[218] routine administration of prophylaxis was not recommended in clean surgery, which includes tympanostomy, tympanoplasty stapedectomy and mastoidectomy. Most of the studies reviewed included both clean and contaminated surgeries. However, in clean-contaminated otologic surgery, such as cholesteatoma and cases of purulent otorrhea, the risk of infection may increase up to threefold.[219] A retrospective study that included dirty or contaminated surgeries in which a single preoperative dose of antibiotic was administered (clindamycin plus ceftazidime or clindamycin plus gentamicin for patients with allergies) observed a significant reduction in postoperative infection (11% vs 1%), although most of the patients in the prophylaxis groups received surgery classed as dirty.[220] Based on the evidence, it is difficult to establish recommendations, although patients undergoing this type of IAC (internal auditory canal) procedure may benefit from a single preoperative dose of antibiotic.

In a meta-analysis conducted by Hochman,[221] the effect of application of topical antibiotics after removing tympanostomy tubes was studied in 1344 patients from 9 randomized studies. A significant reduction in the incidence of postoperative otorrhea was observed in 48% of patients (OR 0.518; 95%CI: 0.39-0.69; p<0.001).

The use of antibiotic prophylaxis in cochlear implant surgery is also controversial. Some guidelines recommend it despite the low rate of infection, because the consequences of infection for the patient are potentially very serious. A recent systematic review[222] identified studies of low quality, using a variety of doses and antibiotics, which made it difficult to make firm recommendations. It concluded by saying that the decision to use perioperative antibiotics should be based on an assessment of the risks to each patient. In general, the incidence of surgical infection is low (3%–4.5%); in 2 studies using a single dose of antibiotics, incidence was 1%.[223,224] A recent case-control study did not find infections, either in patients who received prophylaxis or in those who did not, although the study was retrospective and carried out in a single center.[225] The recommendation of single-dose preoperative antibiotic prophylaxis would be inferred from evidence in clean surgery with implant placement.

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in endoscopic sinus surgery* **(D-I)**.
- *Not recommended in clean otologic surgery* **(D-I)**.
- *Recommended topical application of antibiotic after tympanoplasty* **(A-I)**.
- *Recommended in clean contaminated and contaminated surgery* **(B-III)**.
- *Recommended in cochlear implant surgery* **(B-III)**.

Antimicrobial:

- *In clean contaminated and contaminated surgery: amoxicillin-clavulanic acid* **(B-III)**.
- *In cochlear implant: cefazolin* **(A-II)**.

Beta-lactam allergy:

- *Clean contaminated and contaminated surgery: clindamycin plus gentamicin* **(C-III)**.
- *Cochlear implant: clindamycin or vancomycin* **(C-III)**.

Duration:

- *Single preoperative dose for clean contaminated and contaminated surgery* **(A-II)** *and cochlear implant* **(A-I)**.

5.8.4. Maxillofacial surgery

Septoplasty and rhinoplasty

<u>Search terms</u>: "Antibiotic prophylaxis" AND "Septoplasty/rhinoplasty"

Septoplasty and rhinoplasty are considered clean-contaminated procedures. Septoplasty refers to the removal of the septal cartilage, and rhinoplasty to the removal or remodelling of the nasal cartilages, sometimes with grafts or prostheses. The incidence of infection in both procedures is low. Various controlled clinical trials and meta-analyses were unable to demonstrate the benefit of administering prophylaxis in septoplasty, although in most of the studies, the nasal packing was removed in less than 48 hours.[218] Likewise, 2 controlled clinical trials found no benefit from use of prophylaxis in rhinoplasty, although no distinction was made between simple and complex rhinoplasty (revision surgery, grafts or prosthetic material).[218] A controlled clinical trial involving 100 patients with complex septorhinoplasty found an infection rate of 7.9% in the group that received antibiotic prophylaxis for 12 days vs 18.7% in the placebo group.[226] Two subsequent controlled clinical trials in complex surgery (364 patients) found no differences between administration of a single preoperative dose of prophylactic antibiotics vs. over 7 days.[227,228] .

Nor did a systematic review of the recent literature found no benefits to prolonging prophylaxis with nasal packing.[229]

Hence a preoperative dose of antibiotic prophylaxis could be recommended in complex surgery with insertion of a nasal prosthesis.

Recommendations for antimicrobial prophylaxis

Indication:

- *Septoplasty: Not recommended* **(D-I)**
- *Simple rhinoplasty: Not recommended* **(D-I)**
- *Complex rhinoplasty (revision, prosthesis): Recommended* **(B-II)**

Antimicrobial: *cefazolin* **(B-II)** *or amoxicillin-clavulanic acid* **(B-III)**

Beta-lactam allergy: *vancomycin or clindamycin* **(C-III)**

Duration: *single preoperative dose* **(A-I)**.

Maxillofacial fractures

Search terms: *"Antibiotic prophylaxis" AND "maxillofacial fractures".*

There is limited information about the effect of prophylaxis in surgery for repair of maxillofacial fractures.[230] Systematic reviews, such as the one by Andreasen et al.[231] noted that administration of antibiotic prophylaxis was clearly beneficial, with a statistically significant reduction in infection from 53% to 6% (p=0.001), especially in patients with mandibular fractures, since the frequency of infection in the zygomatic-orbital complex is lower.

A recent meta-analysis of 7 controlled clinical trials and 6 cohort studies of patients undergoing surgery for maxillofacial fractures did not support postoperative administration of antibiotic prophylaxis, compared with preoperative or pre- and perioperative administration,[232] and found no significant differences in the risk of SSI in subgroup analyses of mandibular fractures or open surgical techniques.

Recommendations for antimicrobial prophylaxis

Indication:

Recommended in maxillofacial fractures, especially mandibular fractures requiring open reduction **(A-II)**

Antimicrobial: *cefazolin* **(A-II)** *or amoxicillin-clavulanic acid* **(B-III)**

Beta-lactam allergy: *vancomycin or clindamycin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.8.5. Dental procedures.

Search terms: *"Antibiotic prophylaxis" AND "Tooth extractions" OR "Third molar extraction" OR "Intraoral bone grafting procedures".*

A recent Cochrane review[233] analyzed the findings of 18 controlled studies including 2456 patients who had undergone third molar extraction. The authors observed the possible beneficial effect of antibiotic prophylaxis for reducing infection (NNT = 38) and alveolitis sicca dolorosa (dry socket) (NNT = 38) but confirmed one prophylaxis-related adverse effect in every 21 healthy patients. Similar findings were observed in a recent systematic review,[234] so that antibiotic prophylaxis is not recommended for patients without risk factors for infection, and would only be advisable in patients with risk factors for SSI. Reported risk factors for dry socket infection include age, surgery or previous infection, smoking, systemic diseases, and traumatic extraction.[235,236]

Bacterial contamination at the time of dental implant placement is mentioned as an important factor associated with implant loss, including in the long term. In a recent systematic review,[237] preoperative administration of 2 g of amoxicillin was shown to significantly reduce the risk of dental implant failure, although the effect on surgical infection or adverse effects is less clear.

Lindeboom[238] analyzed the effect of antibiotic prophylaxis on 20 patients who required intraoral bone grafting. In the placebo group, two patients presented infection in the recipient site, one patient in the donor site and two patients in both locations, whereas no infectious complications were noted in the group receiving antibiotic prophylaxis. Hence, antibiotic prophylaxis is recommended in patients requiring intraoral bone grafts. Antibiotic prophylaxis with clindamycin versus penicillin has been compared, with no differences in rates of surgical infection.[239]

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended in intraoral bone graft implantation* **(B-II)**.
- *Not recommended for dental extraction in patients without risk factors* **(D-II)**
- *Not recommended in oral implants or endodontics* **(D-II)**

Antimicrobial: *amoxicillin 1 g, oral* **(A-II)**

Beta-lactam allergy: *clindamycin, oral* **(B-II)**

Duration: *single preoperative dose* **(A-I)**

5.9. Trauma surgery and orthopedic surgery

Search terms: *"Antibiotic prophylaxis" AND "Orthopaedic surgery" OR "Arthroplasty" OR "Fracture" OR "Spine" OR "Amputation".*

Most surgical procedures in traumatology and orthopedics are classed as clean. While rates of surgical infection do not normally exceed 2–5%, the consequences of postoperative complications can be devastating, requiring longer hospital stays, more operations, and very high antibiotic consumption, with a significant impact on the psychological and functional well-being of the patient.[9]

The organisms involved in these infections are mainly those of the skin microbiota. The most frequent are *S. aureus* and coagulase-negative staphylococci, followed by gram-negative bacilli and streptococci.[9] In lower lumber spine surgery and femoral head fracture repair (generally in the elderly), polymicrobial infections with gram-negative involvement are more frequent.[240,241]

5.9.1. Closed fracture reduction without osteosynthesis material and other clean orthopedic surgery without instrumentation.

Antimicrobial prophylaxis is not recommended in patients undergoing clean orthopedic surgery without instrumentation, including simple arthroscopy without ligamentoplasty.[242–244]. There are few recent data with updates on this type of surgery, although some authors recommend considering antibiotic prophylaxis in risk patients (diabetics, the obese or with immunosuppression). There are no studies for ligamentoplasty, although the recommendations for primary arthroplasty could be extrapolated (**B-III**).

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in clean orthopedic surgery without instrumentation* **(D-II)**.
- *Consider the use of prophylaxis in patients with risk factors; it may be considered in ligamentoplasty by referring to recommendations in arthroplasty* **(B-III)**.

5.9.2. Closed fracture reduction with osteosynthesis material.

In most of the studies, prophylaxis was performed with a first- or second-generation cephalosporin,[245–249] or a glycopeptide for patients with beta-lactam allergies, usually vancomycin or teicoplanin. Patients with hip fractures are generally elderly, with comorbidities, and institutionalized. They are often colonized with MRSA,[250] which is frequent in surgical wound infections,[251] although polymicrobial infections with the involvement of gram-negative bacilli are also common.[252] As mentioned in section 4.5, in patients colonized with MRSA, prophylaxis with glycopeptides has not been shown to reduce the overall rate of infection, although it has been more useful in infections caused by resistant staphylococci,[79,80,246] and in some studies, an increase in the overall rate of SSI has even been noted.[81] Prophylaxis with glycopeptides plus a beta-lactam has been shown to reduce the rate of SSI, particularly in conjunction with other decolonization measures or topical decontamination of the patient.[80,82] Hence, in contexts where MRSA infection is highly prevalent or a risk, use of vancomycin or teicoplanin is recommended. If a glycopeptide is used, an antibiotic active against gram-negative bacilli may be added if local epidemiology indicates that these organisms are common (cefazolin or cefuroxime if the patient is not allergic to beta-lactams, and gentamicin if they are). There is no evidence to support change of prophylaxis in patients colonized with multidrug-resistant gram-negative bacteria, although adding gentamicin, for example, may be considered if local epidemiology indicates that these organisms are prevalent. [240,253] Most studies consider that duration of prophylaxis should be ≤ 24h, although 1 preoperative dose may possibly be sufficient.[247,248] A recently performed clinical trial in patients with open reduction of closed fractures compared 83 patients receiving cefazolin <23 h and 77 patients receiving a preoperative dose, with repeat dosing if length of surgery was more than 3 h. and found no significant differences in the rate of infection.[254]

Recommendations for antimicrobial prophylaxis

Indication:

Recommended in closed fracture reduction with osteosynthesis material **(A-I)**

Antimicrobial: *cefazolin or cefuroxime* **(A-I)**.

In case of risk of MRSA SSI: vancomycin or teicoplanin **(B-II)** *plus cefazolin or cefuroxime if there is risk of gram-negative bacteria (GNB) SSI.*

In case of risk of resistant GNB SSI, add gentamicin **(B-III).**

Beta-lactam allergy: *vancomycin or teicoplanin* **(B-II)** *(plus gentamicin in case of risk of GNB SSI)* **(B-III)**

Duration: *≤ 24h* **(A-I)**, *a single dose may be enough* **(A-II)**

5.9.3. Open fracture surgery

Based on the available evidence, antibiotic prophylaxis is indicated for open fracture surgery.[255,256] The risk of infection increases with the degree of complexity of the open fracture, as defined by the Gustilo classification. Antibiotic prophylaxis should be started as soon as possible, since prompt administration of the first dose of antibiotic, (as measured from time of injury, not time of admission to the emergency department) is associated with reduced rates of surgical infection (administration is recommended within the first 3 h following the injury).[257,258] Duration of prophylaxis and antibiotic type are not well established, since the quality of the available evidence is limited.[259–262] A clinical trial performed on Gustilo Grade II fractures found no differences in infection rate after administration of prophylactic cefuroxime plus gentamicin for 24 hours or for 5 days after surgical debridement.[262] A systematic review of the literature suggests that prolonging prophylaxis for more than 24 hours does not reduce the risk of SSI,[259] although the data are very limited. Another meta-analysis on 5 comparative (1,284 open fractures) and 27 observational (5,408 fractures) studies found no differences between more or less than 72 hours, or between more or less than 24 hours, classifying by Gustilo open fracture type, but again the data are limited.[263] Based on the available evidence, for Grade I and II fractures, administration of prophylaxis for up to 24 h after debridement would be sufficient, and for Grade IIIA fractures for a maximum of 72 hours, or until soft tissue closure (whichever occurs first). Most studies use first-generation cephalosporins, adding an aminoglycoside for Grade III fractures to provide coverage against gram-negative bacteria; there are no well-designed comparative studies. In an unblinded controlled clinical trial, Saveli et al[261] compared cefazolin (n=65) and cefazolin plus vancomycin (n=65) until 24 h after fixation of the fracture, without finding differences in infection rates. In a retrospective study of grade III fractures, the authors compared cefazolin plus gentamicin (n=37) with piperacillin-tazobactam (n=35), without finding differences. [260] A recently published retrospective study in patients with Grade III fractures compared prophylaxis with cefazolin (n=65) with cefazolin and an aminoglycoside (n=61) and found a significant increase in acute kidney injury in the aminoglycoside group (4% vs 10%) and no differences in rates of wound infection. There were no differences in time of administration (in the initial assessment 94% vs 91%) or in duration of prophylaxis (66 h vs 72 h).[264] In another retrospective study, adding gentamicin to cefazolin did not reduce the incidence of infection, but did not lead to acute kidney injury; AKI was associated with the presence of hypotension on admission and surgical site infection.[265] On the other hand, in a study including 1004 military personnel with combat-related open extremity fractures, the addition of quinolones or aminoglycosides to cefazolin, clindamycin or amoxicillin-clavulanic acid prophylaxis was associated with a lower rate of surgical wound infection, but not of osteomyelitis.[266] In the absence of further evidence, a first or second-generation cephalosporin can be recommended for Grade I and II fractures or amoxicillin-clavulanic acid, with additional coverage against gram-negative bacteria (aminoglycoside in a single daily dose) for Grade IIIA fractures. Patients with Grade III-B and C fall outside the scope of prophylaxis and require antibiotic treatment. Open fractures usually require initial surgical debridement and subsequent reoperations are often needed to ensure definitive fixation +/- soft tissue closure (grade IIIB fractures). For Grade III open fractures (particularly IIIB), the (modified) recommendations of the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)[267] may be considered, although there are no studies validating the approach:

- Amoxicillin-clavulanic acid 2g/8h or a first- or second-generation cephalosporin/8h to start as soon after the injury as possible (<3h) and to continue until soft tissue closure or for a maximum of 72 h (whichever is sooner)
- At the 1st debridement, add gentamicin (5 mg/kg single dose – adjusted bodyweight) to the previous regimen
- During the hour prior to fracture stabilization surgery and soft tissue closure, administer a single dose of vancomycin 15 mg/kg or teicoplanin 800 mg plus gentamicin (single dose of 5 mg/kg – adjusted body weight).

Two systematic reviews of non-comparative studies,[268,269] one of them with a clinical trial of only 62 cases,[269] found a significant reduction in the SSI rate using local antibiotic administration as an adjunct to systemic antibiotic therapy, particularly in grade III-B and C fractures. However, the heterogeneity of the studies makes it difficult to provide specific recommendations.

Recommendations for antimicrobial prophylaxis

Indication:

Recommended in open fracture surgery **(A-I)**

Antimicrobial: *cefazolin* **(A-I)** *or amoxicillin-clavulanic acid* **(B-III)** *(Gustilo grade I and II fractures), add an aminoglycoside (gentamicin) in Gustilo grade III fractures* **(B-II)**.

Beta-lactam allergy: *Vancomycin or clindamycin ± gentamicin* **(B-III)**

Duration: *Start as soon as possible. In Gustilo grade I-II fractures, maintain until 24 hours after debridement* **(A-II)** *and in grade III-A fractures, up to 72 hours maximum, or until soft tissue closure (whichever occurs first)* **(B-III)**

5.9.4. Removal of orthopedic implants used for the stabilization of fractures.

In this type of surgery, the administration of antibiotic prophylaxis has traditionally been considered unnecessary, since it is considered a clean surgical procedure not involving implant placement. In a recent clinical trial, administration of a single preoperative dose of 1 g of cefazolin was not associated with a reduction in the incidence of SSIs associated with removal of orthopedic implants used for treatment of fractures below the knee. There are no data therefore to endorse this practice.[270] In that study, the overall percentage of infections was much higher than expected for a clean surgery (14%). It is currently unclear whether antibiotic prophylaxis with a 2g dose of cefazolin (the current dose recommended for patients > 60 kg) would be effective.

Recommendations for antimicrobial prophylaxis

Indication:

Not recommended in removal of orthopedic implants **(D-II)**

5.9.5. Arthroplasty (THR, TKR, tumor megaprostheses, primary and revision).

Antibiotic prophylaxis with a first- or second-generation cephalosporin has been shown to reduce the rate of surgical site infection.[49,62,271,272] In cases of beta-lactam allergy, different guidelines have recommended giving vancomycin, teicoplanin and clindamycin. In a population-based study of patients who had undergone knee arthroplasty, in which 72,223 patients received cloxacillin prophylaxis and 5771 received clindamycin, more revisions due to infection were observed in the clindamycin group.[273] In several meta-analyses and systematic reviews, glycopeptides were shown to be no more effective than beta-lactams for reducing infections in arthroplasty surgery,[49,274] or orthopedic surgery in general[89,90]and even increased the risk of infection.[275,276] A retrospective cohort study noted a decrease in MRSA and MSSA infection when teicoplanin was added to standard cefuroxime prophylaxis.[277] In another retrospective study (n=1528) performed in a center where MRSA was prevalent (30%), the addition of vancomycin as a prophylactic agent did not reduce the overall rate of surgical wound infections, but did appear to reduce the rate of MRSA infections.[278] However, in a propensity score-adjusted retrospective study including 33,848 patients, the addition of vancomycin to a beta-lactam did not reduce the overall incidence of SSIs or MRSA infections, and was associated with an increased risk of AKI. [91] Owing to the increase in the prevalence of infections caused by gram-negative bacilli, especially in hip arthroplasty, adding an aminoglycoside such as gentamicin to the usual prophylaxis has been considered,[253] but more studies are needed before this approach can be recommended, which has in any case been associated with increased acute kidney injury.[279] Concerning duration of antibiotic prophylaxis in primary arthroplasty, a recent meta-analysis including 4 controlled clinical trials and 4036 patients found no differences in the rate of infection between those who received postoperative prophylaxis or a single preoperative dose (3.1% vs 2.3% respectively).[63] Other retrospective studies[28,280] following the recommendations of the CDC guidelines[5] did not find differences either. Given the heterogeneity of the studies and their low statistical power, the *Proceedings of International Consensus on Orthopedic Infections* did not pronounce either in favor or against the recommendation of a single preoperative dose, pending the results of a randomized clinical trial still in progress.[281] As this document was being completed, a meta-analysis of 23 RCTs and 9 observational studies in arthroplasty found that prophylaxis was more beneficial than non-prophylaxis, but did not find differences in the incidence of infection when a single preoperative dose was given versus more than one dose. No differences were found when first-generation cephalosporins were compared with other antibiotics, although there was heterogeneity among the studies with a high risk of bias.[282]

In cases of revision arthroplasty,[283] and particularly in cases of tumor megaprosthesis reconstruction, some studies suggest more prolonged administration, [284,285] but owing to their retrospective nature, a recommendation for prophylaxis beyond 24 h cannot be made. The risk of infection, and of infections with MDROs, increases in the second stage of a two-stage exchange for prosthetic joint infection. In view of this, broad-spectrum antibiotic prophylaxis is recommended, such as a glycopeptide and a beta-lactam with antipseudomonal activity, to provide coverage against the organism that caused the initial PJI, as well as others likely to cause infection.[281]

In cases where a deep cemented prosthesis is used, the data published suggest that antibiotic-impregnated bone cement reduces the risk of deep infection.[286] The greatest benefit was observed in studies performed with gentamicin.

Recommendations for antimicrobial prophylaxis

Indication:

Recommended in arthroplasties **(A-I)**

Antimicrobial: *cefazolin or cefuroxime* **(A-I)**.

Beta-lactam allergy: *Vancomycin or teicoplanin* **(B-II)** *(plus gentamicin in case of risk of GNB SSI)* **(B-III)**

Duration: *≤24h* **(A-I)**; *possibly a single dose is enough* **(A-II)**. *In megaprosthesis: ≤24 hours* **(A-II)**.

5.9.6. Laminectomies and discectomies, with/without instrumentation

A meta-analysis of 6 controlled clinical trials and a controlled clinical trial in orthopedic spine surgery showed that antibiotic prophylaxis was effective in reducing the rate of SSIs relative to placebo controls.[287,288] The available evidence supports the use of prophylaxis in surgery with and without instrumentation, including fusion surgery, laminectomies and minimally invasive spine surgery.

No one antimicrobial agent is notably more effective for spine surgery procedures. Those most widely studied are the first- and second-generation cephalosporins. Cefazolin would be recommended because of its narrower spectrum, reserving cefuroxime for cases where there is risk of polymicrobial infections.[9]

Most of the studies have demonstrated that a prophylactic regimen of ≤24h is as effective for preventing surgical infection as one of longer duration,[289–293] and that it is not necessary to maintain prophylaxis until the drains are removed.[289,291] A single preoperative dose may be suffiecient,[287,293–295] since low SSI rates have been observed with single dose versus placebo.[287,288]

In cases of beta-lactam allergy, administration of vancomycin, teicoplanin or clindamycin[9] is recommended along with an antibiotic active against gram-negative bacilli, especially when these organisms are commonly present.[296] In this context, the most frequent causes of infection in lumbar and sacral spine procedures are gram-negative bacteria and polymicrobials; in revision surgery, infections caused by multidrug-resistant organisms are more frequent, methicillin-resistant staphylococci in particular.[241] If In case of risk of MRSA, vancomycin or teicoplanin is recommended (taking into account the considerations in section 5.9.3).

A meta-analysis evaluated local application of vancomycin powder to the wound at the end of the procedure. Overall, the pooled data showed a significantly reduced risk of surgical infection. This meta-analysis included a clinical trial and 13 retrospective observational studies, with considerable variability among them.[297] The addition of local application of vancomycin may be considered to reduce the risk of surgical infection in procedures with a higher incidence of staphylococcal infection.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in vertebral orthopedic surgery with/without instrumentation, including vertebral fusion, laminectomy and minimally invasive discectomy* **(A-I)**

Antimicrobial: *cefazolin or cefuroxime* **(A-I)**

Beta-lactam allergy: *vancomycin, teicoplanin* **(B-II)** *(plus gentamicin in case of risk of GNB SSI)* **(B-III)**

Duration: *≤24h* **(A-I)***; a single dose may possibly be enough* **(A-II)**

5.9.7. Limb amputation

Antibiotic prophylaxis is indicated for lower limb amputation. A first- or second-generation cephalosporin or amoxicillin-clavulanic acid are possible alternatives.[298]

There is barely any evidence on duration of prophylaxis. One study (with a quasi-experimental design and a small sample size) suggested that extending prophylaxis duration beyond 24h may reduce the rate of infection.[299] The IDSA guidelines for the diagnosis and treatment of diabetic foot infections[300] make a weak recommendation of 2 to 5 days of prophylaxis in these patients when an amputation is performed that leaves no remaining infected tissue. In the absence of further evidence on this point, a recommendation can be made to administer prophylaxis for at least 24 hours, provided that no infected tissue remains post-amputation.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in amputation of lower limbs* **(A-II)**

Antimicrobial: *cefazolin or cefuroxime or amoxicillin-clavulanic acid* **(A-II)**

Beta-lactam allergy: *Vancomycin or teicoplanin plus gentamicin* **(B-III)**

Duration: *at least 24 hours, provided there is no infected tissue remaining post-amputation* **(B-III)**

5.10. Thoracic surgery

5.10.1. Major and minimally invasive thoracic surgery

<u>Search terms</u>*: "Antibiotic prophylaxis" AND "Non-cardiac thoracic surgery" OR "Antibiotic prophylaxis" AND "Thoracic surgery" OR "Lung surgery"*

Thoracic surgery includes major procedures such as lobectomies and pneumonectomies, atypical resections and thoracotomies. There are also less invasive procedures such as videothoracoscopy (VATS), mediastinoscopy, and thoracic tube placement.

The most common infections in these patients are surgical site infections, pneumonias and empyemas. In general, these are clean surgeries with a low infection index (< 2%), and this is usually lower in minimally invasive procedures than in open surgery.

The organisms most commonly involved in these infections are gram-positives (*S. aureus* and *S. epidermis*), although gram-negative bacteria (*H. influenzae, K. pneumoniae, Enterobacter* spp*, Acinetobacter* spp, etc.) and fungal pathogens are also found in cases of nosocomial pneumonia.

There is no general consensus about the best antibiotic agent to use, although in general, cefazolin (2 g single dose, i.v) is widely accepted (together with amoxicillin- clavulanic acid) and vancomycin or clindamycin are considered good alternatives for patients allergic to beta-lactams. By inferring from evidence found in cardiac surgery, vancomycin is advised for MRSA-colonized patients (see sections 4.5 and 5.1).

Prophylaxis is consistently recommended for patients undergoing major thoracic surgery, with strength of evidence A, since there are randomized clinical trials that have demonstrated that its beneficial effect compared to placebo. [301,302] There is less evidence for minimally invasive surgery, although because the procedures are the same, prophylaxis can be generalized from major thoracic surgery.

One randomized controlled trial demonstrated that extended prophylaxis (48 hours) in patients who underwent elective thoracic surgery requiring tube thoracostomy did not reduce the number of postoperative infectious complications compared with preoperative prophylaxis (single dose of cefazolin).[303]

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended in major thoracic surgery* **(A-I)**.
- *Recommended in minimally invasive thoracic surgery (videothoracoscopy, mediastinoscopy)* **(B-III)**

Antimicrobial: *cefazolin for major thoracic surgery* **(A-I)** *and minimally invasive thoracic surgery* **(A-II)**

Beta-lactam allergy: *vancomycin/teicoplanin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.10.2. Tube placement, penetrating chest trauma

Search terms: *"Antibiotic prophylaxis" AND "Thoracostomy" OR "Tube thoracostomy" AND "Penetrating thoracic injuries".*

In procedures such as elective tube thoracostomy, there is no evidence to recommend routine prophylaxis.

The situation in blunt and penetrating chest trauma remains controversial, with contradictory findings in the published literature, including retrospective studies,[304] randomized studies,[305,306] and meta-analyses.[307,308] Overall, the studies demonstrate, with strength of evidence A, that antibiotic prophylaxis is beneficial in tube thoracostomy for penetrating chest trauma. In cases of penetrating chest trauma classed as dirty, empiric antibiotic therapy is indicated and not prophylaxis alone.

Based on the studies cited, duration of prophylaxis is a single preoperative dose.

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in elective thoracic tube placement* **(D-II)**
- *Recommended in penetrating chest trauma* **(A-I)**

Antimicrobial: *cefazolin* **(A-I)**

Beta-lactam allergy: *vancomycin/teicoplanin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.11. Esophageal, gastric or duodenal surgery

There is a high risk of infection in gastroduodenal surgery when there is decreased gastric acid production and gastrointestinal motility, factors which, in normal conditions, inhibit bacterial growth in the stomach and duodenum. Patients at risk include those with gastric outlet obstruction, gastric bleeding, gastric ulcers, tumors and anti-secretory therapy that increases the gastric pH, which includes most of the patients undergoing surgery in this part of the digestive system.

The organisms most frequently isolated in upper gastrointestinal tract pathologies are coliform bacteria (*E. coli*, *Proteus* sp, *Klebsiella* sp), staphylococci, *S. viridans*, *E. faecalis* and occasionally *Clostridium* sp., *Bacteroides* sp, *Candida* sp. The normal esophagus only has transit bacteria. Nevertheless, certain situations (stenosis, stasis) favor bacterial colonization and antibiotic prophylaxis should be considered for this reason in surgery for benign or malign stenosis, achalasia and gastroesophageal reflux.

5.11.1. With rupture of the mucosa (esophagectomy, gastrectomy, cephalic pancreato-duodenectomy)

Search terms: *"Antibiotic prophylaxis" AND "Oesophageal surgery" OR "Gastrectomy" OR "Pancreatoduodenectomy".*

There is no high-quality evidence on antibiotic prophylaxis in esophageal surgery and recommendations are inferred from evidence in gastric surgery. Several clinical trials have demonstrated the effectiveness of prophylaxis in gastric and gastroduodenal surgery.[309,310] The most widely used antibiotics have been first- or second-generation cephalosporins, but beta-lactam/beta-lactamase inhibitors have also been used with similar results.[311] A single dose has been shown to be as effective as more prolonged prophylaxis with 1st and 2nd generation cephalosporins.[312–314] In a recent clinical trial, amoxicillin-clavulanic acid was just as effective over 24 hours as 72 hours.[315]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in esophageal surgery* **(A-II)***, gastric* **(A-I)** *and gastroduodenal* **(A-I)** *surgery.*

Antimicrobial: *cefazolin* **(A-I)**

Beta-lactam allergy: *vancomycin or clindamycin plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.11.2. Without mucosal rupture (gastroesophageal reflux surgery, achalasia, vagotomy)

Search terms: *"Antibiotic prophylaxis" AND "Antireflux surgery" AND "Vagotomy".*

There are no specific studies on antibiotic prophylaxis in this type of procedure, so that recommendations have been extrapolated from previous studies on similar patients and in similar situations.[9] Given that there is no opening of mucosa, these procedures can be regarded as clean surgery and administration of prophylaxis is not therefore systematically recommended. However, prophylaxis is considered acceptable in high-risk patients, such as the morbidly obese, patients with intestinal obstruction, hypochlorhydria, gastrointestinal bleeding, tumors, perforation, immunosuppression or ASA≥3. In these cases, the prophylaxis indicated would be the same as that prescribed for EGD procedures with rupture of the mucosa.

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in esophageal-gastric-duodenal surgery without mucosal rupture* **(D-II)***.*
- *Recommended in esophageal-gastric-duodenal surgery without mucosal rupture in high-risk patients* **(C-III)***.*

Antimicrobial: *cefazolin* **(A-I)**

Beta-lactam allergy: *vancomycin plus gentamicin or clindamycin plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.11.3. Percutaneous endoscopic gastrostomy (PEG) placement

Search terms: *"Antibiotic prophylaxis" AND "Percutaneous endoscopic gastrostomy".*

Two meta-analyses[316,317] and various clinical trials[318–322] have shown that peristomal wound infections are reduced when prophylaxis is given before the procedure. Different antibiotic regimens have been used, principally cephalosporins and penicillins/beta-lactamase inhibitors. There was a striking difference in the number of infections in the placebo group. Most studies did not report the causative organism. One study compared prophylaxis alone versus prophylaxis combined with preoperative use of a local antiseptic and found a greater reduction in SSI in the latter, although the sample size was small.[323] Recent studies using a new technique for PEG insertion showed similar infection rates in groups treated and not treated with antibiotics.[324,325]

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended in PEG implantation* **(A-I)**
- *Recommended a good antisepsis at implantation site* **(A-III)**

Antimicrobial: *cefazolin or cefuroxime or amoxicillin-clavulanic acid* **(A-II)**

Beta-lactam allergy: *vancomycin plus gentamicin or clindamycin plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.12. Bariatric surgery

Search terms: *"Antibiotic prophylaxis" AND "Bariatric surgery".*

No well-designed studies have evaluated the efficacy of antibiotic prophylaxis in bariatric surgery, apart from one study on laparotomy, which showed the efficacy of cefazolin versus placebo.[326] Most bariatric surgery is currently performed laparoscopically, which has reduced the rate of SSIs. The studies of prophylaxis in recent years have been carried out to compare different antibiotics and doses. A study of cases and controls[327] and two observational studies[328,329] showed that use of antibiotics different from cefazolin is associated with a higher risk of infection. By extrapolating from similar procedures, bariatric surgery is a clean-contaminated technique and would require systemic antibiotic prophylaxis. In these patients, it is recommended to adjust the antibiotic dose according to weight (see section 3.3).

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in bariatric surgery* **(A-II)**

Antimicrobial: *cefazolin or cefuroxime or amoxicillin-clavulanic acid* **(A-II)**

Beta-lactam allergy: *vancomycin plus gentamicin or clindamycin plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.13. Small bowel surgery

<u>Search terms</u>*: "Antibiotic prophylaxis" AND "Small bowel surgery" AND "Small bowel transplantation".*

Small bowel surgery covers incisions or resections of the small intestine, including enterotomy, intestinal bypass and stenosis surgery.

There are no randomized clinical trials in antibiotic prophylaxis for small bowel surgery, although since it is clean-contaminated surgery, prophylaxis is recommended by inference from evidence in other types of surgery, particularly colorectal. The recommendations are those adopted by the IDSA, SIS and SHEA, with expert opinion.[9,116] The organisms most frequently isolated from surgical wounds in small bowel surgery are gram-negative bacilli (aerobes and anaerobes) of intestinal origin, as well as gram-positive cocci (streptococci, staphylococci and enterococci). Bacterial densities are variable, ranging between 10^1 to 10^3 CFU in the duodenum and 10^4 to 10^7 CFUs in the jejunum and ileum.[330]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in small bowel surgery with and without obstruction* **(A-III)**

Antimicrobial:

- *In surgery without obstruction: cefazolin* **(A-I)***.*
- *In surgery with obstruction: cefazolin plus metronidazole* **(B-II)** *or amoxicillin-clavulanic acid* **(B-III)**

Beta-lactam allergy:

- *In surgery without obstruction: clindamycin plus gentamicin* **(B-III)***.*
- *In surgery with obstruction: metronidazole plus gentamicin* **(B-II)***.*

Duration: *single preoperative dose* **(A-I)**

5.14. Other digestive surgery

5.14.1. Splenectomy

<u>Search terms</u>*: "Antibiotic prophylaxis" OR "Splenectomy".*

Non-traumatic splenectomy is considered clean surgery and routine antibiotic prophylaxis is not indicated. Some authors recommend it in high-risk patients: immunocompromised individuals or those under immunosuppressive therapy, in elderly patients with debilitating diseases, when surgery is longer than 120 minutes or there is excessive blood loss.[331] Traumatic splenectomy is not considered a clean procedure and prophylaxis must be considered. By inference from evidence in other surgery, the recommended prophylaxis is a single preoperative dose of cefazolin, using clindamycin and gentamicin for beta-lactam allergic patients.

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in splenectomy without risk factors* **(D-II)**.
- *Recommended in traumatic or elective splenectomy with risk factors* **(B-III)**

Antimicrobial: *cefazolin* **(A-I)**

Beta-lactam allergy: *vancomycin plus gentamicin or clindamycin plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.14.2. Penetrating abdominal trauma

Search terms: *"Antibiotic prophylaxis" AND "Abdominal penetrating trauma" OR "Trauma surgery".*

There is currently no information from controlled clinical trials that supports or refutes the use of antibiotic prophylaxis in penetrating abdominal trauma.[332] In one of the few studies that compared antibiotic prophylaxis with placebo, SSI rates of 7%, 33% and 30% were obtained with preoperative, perioperative and postoperative prophylaxis, respectively.[333] When the injury affected the colon, the percentages of infection were higher (11%, 57% and 70% in each of the respective groups).

No studies have been found to demonstrate the need to continue antibiotics for more than 24 hours after surgery, if the surgery was performed within the first 12 hours after the trauma occurred. Guidelines published in 2000 and updated in 2012 carried out a systematic review of the literature (44 studies) to evaluate the evidence on optimal antibiotic regimens and their duration[334,335] and concluded, with level 1 evidence, that all patients with penetrating abdominal trauma should be given a preoperative dose of antibiotics with coverage against aerobes and anaerobes, and that prophylaxis should be maintained for no more than 24 hours in the presence of a hollow viscus injury in patients with acute trauma. Based on level 3 evidence, the antibiotic dose should be 2-3 times higher in patients with hemorrhagic shock and be repeated after transfusion or every 10 units of transfused blood until bleeding ceases. After 24 hours, the risk of bacterial resistance increases, as does mortality due to infections caused by multidrug-resistant organisms.[61]

Administration of a single antibiotic with activity against aerobes and anaerobes would appear to be the most cost-effective strategy. A 1991 meta-analysis showed no differences in infection rates between prophylaxis with beta-lactam monotherapy versus aminoglycoside combination therapy, although many of the antibiotics used in those trials are not currently used.[336]

In a retrospective study reviewing the microbiological profile of infections after penetrating abdominal trauma (75% colon and 25% small bowel), *E. coli* was the most frequently isolated species (55%), followed by *Enterobacter cloacae* (26%), *Klebsiella spp*. (17%) and *Proteus mirabilis* (4%).[337] *E. coli* and *Bacteroides* spp. were predominant in colon injuries and *Enterobacter* and *Klebsiella* in stomach and small bowel injuries.[337] The second most common organism was *Enterococcus*, found in 20% of infections. Based on the published findings and taking into account the most likely microbiology and local resistance profiles, amoxicillin-clavulanic acid or cefoxitin/cefazolin/cefuroxime plus metronidazole are options, with gentamicin plus metronidazole in case of beta-lactam allergy.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in penetrating abdominal trauma* **(A-I)**

Antimicrobial: *cefuroxime plus metronidazole* **(A-I)** *or amoxicillin-clavulanic acid* **(A-II)**

Beta-lactam allergy: *metronidazole plus gentamicin* **(A-III)**

Duration: *single preoperative dose* **(A-I)***; if hollow viscus injury, ≤24 hours* **(A-II)**

5.15. Appendicectomy

Search terms: *"Antibiotic prophylaxis" AND "Appendicectomy" OR "Surgery for appendicitis".*

Use of antibiotics as prophylaxis in appendicectomy is fully determined by the presence or not of one of the variants of complicated acute appendicitis (abscess formation, plastron appendicitis, diffuse peritonitis or perforation). Nevertheless, even in uncomplicated cases requiring surgical intervention (between 80–85% of cases), it is recommended to use antibiotic prophylaxis owing to the presence of the organisms that habitually cause complicated clinical pictures (principally *E. coli* and *Bacteroides fragilis*).[338] While the rate of SSIs in cases of uncomplicated appendicitis is generally low and should not exceed 5%, laparoscopic appendicectomy reduces these figures even further.

Paradoxically, some series have linked the minimally invasive approach to higher rates of organ/space SSI.[9]

Most comparative studies of different antimicrobial approaches were carried out before 1990.[9]

Use of antibiotics as prophylaxis in uncomplicated appendicectomy (and complicated, even if is treated as an intra-abdominal infection) significantly reduces the rate of SSI compared with placebo.[339] Nevertheless, no antibiotic that is clearly superior to the rest has yet been identified. The agent should provide coverage against enteric aerobic organisms and anaerobes. At present there is no evidence in uncomplicated appendicectomy (phlegmonous and gangrenous) to support the use of antibiotics beyond the initial dose.[17,340,341] A perforated appendicitis requires antibiotic treatment, which may be short-term (24–72 hours).[340,342]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in uncomplicated appendectomy* **(A-I)**

Antimicrobial: *cefuroxime plus metronidazole* **(A-I)** *or amoxicillin-clavulanic acid* **(A-II)**

Beta-lactam allergy: *metronidazole plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.16. Colorectal surgery

Search terms: "Antibiotic prophylaxis" AND "Elective colorectal surgery" OR "Laparoscopic colorectal surgery" OR "Resection for colorectal cancer".

Colorectal surgery has the highest rates of SSI in gastrointestinal surgery, with a frequency of approximately 17-20% when recorded prospectively. Elective colorectal surgery can be considered clean-contaminated, although it may become contaminated during the surgical procedure. The use of antibiotic prophylaxis reduces rates of infectious complications from 30% to below 10%. Among the different procedures, rectal resection (especially with a perineal phase) has one of the highest rates of SSI. [9] While widespread use of the laparoscopic approach has helped reduce the onset of infection,[343] other factors, such as length of surgery, malnutrition, immunosuppression, perioperative transfusion, hypothermia, hyperglycemia and obesity help increase the risk of SSI in these patients. The organisms involved are the those found in the large intestine itself (gram-negative aerobes and anaerobes), where the proportion of anaerobes is much higher than in other sections of the digestive tract.[151,344]

Antibiotic prophylaxis prior to elective colorectal surgery significantly reduces the risk of surgical wound infection.[21] The recommended antibiotics should include coverage of anaerobes. There is a good deal of heterogeneity in the studies and it is impossible to find clear evidence on duration, timing of administration, the impact of choice of approach or patient characteristics, dosing, frequency or the possibility of secondary effects.[31,275,345,346]

It is difficult to make definitive recommendations because of the large number of prophylactic regimens used, as well as the scarcity of high-quality comparative studies. The choice of antibiotic was based on seeking coverage of gram-negatives and anaerobes, using various combinations of metronidazole with second- and third-generation cephalosporins.[347–351] The appearance of ertapenem led to a series of case studies, some with conflicts of interest, which showed the superiority of ertapenem to all the previously proposed combinations.[352,353] However, the increase in *C. difficile* infections and the danger of using a potentially useful agent in infections caused by MDROs raises questions about the applicability of the results of these studies.

In general, most of the recent studies justify single-dose prophylaxis or not prolonging administration beyond 24 h.[21,60] A case-control study[354] and a systematic review of the literature[5] found no differences between single-dose and multiple-dose prophylaxis, regardless of whether oral prophylaxis was used.

Likewise, in cases where surgery is prolonged (the traditional limit of 3h is based on studies from the 1980s)[60] or significant blood loss, the dose should be repeated. Pharmacokinetic studies recommend intraoperative redosing if surgery is very long or in the case of high creatinine clearance.[52,53]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in colorectal surgery* **(A-I)**

Antimicrobial: *cefuroxime plus metronidazole or amoxicillin-clavulanic acid* **(A-II)** *(add gentamicin in case of high prevalence of resistant GNB)* **(B-III)**

Beta-lactam allergy: *metronidazole plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

Oral antibiotic prophylaxis and mechanical bowel preparation

Search terms: *"Antibiotic prophylaxis" AND "Colorectal surgery" AND "Preoperative oral antibiotic prophylaxis".*

Mechanical bowel preparation (MBP) in isolation is not an effective measure for reducing the rate of infection or preventing suture dehiscence. On the other hand, data generated by randomized studies, the meta-analyses that included them, as well as observational studies suggest that oral antibiotics combined with MBP play a crucial role in reducing the risk of superficial, deep and organ/space SSIs, preventing suture dehiscence, postoperative ileus, readmissions and mortality, without being associated with increased risk of *C. difficile* infection. [355–358]

Oral prophylaxis used to be based on administering non-absorbable antibiotics, such as erythromycin base, which is some cases, is no longer marketed. At present, some of the combinations used include absorbable antibiotics such as metronidazole or ciprofloxacin.[359] The most widely used oral combinations are neomycin or kanamycin plus metronidazole or erythromycin base.[360,361]

The role of oral antibiotics in the absence of MBP has only been studied in the context of observational studies.[362] The results of randomized prospective studies in progress, analyzing the effect of oral antibiotics without mechanical preparation, may throw up valuable information on this topic.[363]

Since current evidence comes from studies combining oral antibiotics with MBP, it is difficult at the moment to justify performing elective colorectal surgery without appropriate MBP, which would include oral antibiotic prophylaxis. Oral prophylaxis should be administered in a suitable time gap after mechanical bowel preparation, and distributed in three doses to be ingested 19, 18 and 9 hours before the start of surgery.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in mechanical bowel preparation* **(A-II)** *associated with oral antibiotics* **(A-I)** *in elective colorectal surgery.*

Antimicrobial: *Neomycin 1000 mg plus metronidazole 500 mg), 3 preoperative doses 19, 18 and 9 hours before the start of the procedure* **(A-II)**.

5.17. Hepatobiliary and pancreatic surgery

Search terms: *"Antibiotic prophylaxis" AND "Cholecystectomy" OR "Hepatopancreatobiliary surgery" OR "Hepatectomy" OR "Liver or hepatic resection" OR "Biliary tract surgery or reconstruction" OR "Pancreaticoduodenectomy" OR "Pancreatectomy".*

Biliary tract surgery includes cholecystectomy, bile duct exploration procedures and choledochoenterostomy. The most commonly found organisms in infection after biliary tract procedures are *E. coli* and some species of *Klebsiella* and enterococci, less frequently streptococci and staphylococci, and occasionally anaerobes, mainly *Clostridium* spp.[364–371] The smaller incisions required in laparoscopy are associated with decreased rates of SSI, [372,373] so that administration of prophylaxis is only indicated in high-risk patients. [369,371,374–379] 'High-risk' in this context includes emergency procedures for acute illness,[364,365,380–385] immunosuppression,[386] diabetes,[380,381,383,384] pregnancy,[364,384] procedure >120 minutes,[365,387] age >70 years,[388] open cholecystectomy[385,389] conversion of laparoscopic to open cholecystectomy,[382,383] ASA≥3,[365,380–383,385,388,389] episode of biliary colic within 30 days prior to the procedure, jaundice, choledocholithiasis, cholangitis, previous biliary surgery, acute cholecystitis within the previous 6 months, pancreatic lithiasis, gallbladder prosthesis[365,380–386,388] and antibiotic therapy within the previous month.

5.17.1. Cholecystectomy and biliary surgery

Prophylaxis does not appear to be necessary in low-risk patients undergoing laparoscopic cholecystectomy, but should be considered in all high-risk situations.[390] Various trials compared a single dose at induction of anesthesia[387,388,391] with 2, 3, or up to 6 doses at different times after the intervention[365,374,378,392,393] and found no differences between them, except for Matsui Y et al[380] who observed fewer infectious complications and postoperative costs with 3-dose prophylaxis (24 h). One trial[394] compared routes of administration (oral versus intravenous) and found no differences in infection rates. A meta-analysis of 12 clinical trials by Yan RC et al[384] found no differences in rates of SSI. The most widely studied antimicrobials as prophylactic agents are first-generation, [366,368,393,395]second-generation[369,374,375,393,395,396] and third-generation cephalosporins[364], with no significant differences between them. Most of the clinical trials were performed on small numbers of patients,[397,398] although one was recently published that included 570 patients, without finding a beneficial outcome from prophylaxis.[395] A recent systematic review and reappraisal of previously reported meta-analyses, excluding RCTs that did not meet the criteria, found data in favor of prophylaxis, but only one of the RCTs included, unblinded and with a high risk of bias, showed the benefit of prophylaxis.[399]

In summary, the current evidence does not support prophylaxis in low-risk patients undergoing elective laparoscopic cholecystectomy, even with incidental rupture of the gallbladder (level A evidence against prophylaxis for low-risk patients). Antibiotic prophylaxis should be considered in patients at a high-risk for infection, and includes the open approach or with a high risk of conversion to open procedure (level A for prophylaxis in high-risk patients).

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in low-moderate elective laparoscopic cholecystectomy* **(D-I)**.
- *Recommended in open cholecystectomy* **(A-I)** *or high-risk laparoscopic cholecystectomy* **(A-II)**.

Antimicrobial: *cefazolin* **(A-I)**

Beta-lactam allergy: *vancomycin plus gentamicin or clindamycin plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.17.2. Hepatic surgery

Hepatic surgery has been classed as clean-contaminated because of bile duct transection. In referral hospitals, mortality is generally less than 5%, but infection rates can reach 20-25%.[400]

Various clinical trials have not found any benefit from the administration of surgical antibiotic prophylaxis. The 1998 study by Wu et al.[401] used cefazolin associated with gentamicin for 7 days and found no differences in postoperative infection rates when compared with the placebo group, although they excluded patients with synchronous metastasis or requiring immediate hepatectomy. In a 2013 publication, Hirokawa reached the same conclusion by postoperative comparing antibiotics over 3 days,[402] and Zhou et al[403] did not find differences either after comparing placebo with preoperative cefuroxime prophylaxis in patients scheduled to undergo elective hepatectomy. However, most of these included patients with simple hepatectomy (1–3 segments of the liver) rather than major hepatectomy including extrahepatic bile duct resection, sometimes with cholangiojejunostomy, which is associated with greater risk of infection.

A number of risk factors associated with infection following hepatectomy have been reported:[400,403–411] Age > 70 years, operation time >300 minutes, blood transfusion,[400,411] degree of hepatectomy, presence of previous biliary drainage, preoperative jaundice and cirrhosis. In robot-assisted laparoscopic liver surgery, the rate of organ/space SSI is similar to open surgery, although the rate of superficial and deep wound surgical infections is lower.[412]

With respect to duration of prophylaxis, a blinded, prospective randomized three-year study[400] recruiting 180 patients found no differences between 2-day vs 5- day prophylaxis; nor did Sugawara et al.[413] when they compared 2-day vs 4-day administration of prophylaxis.

In spite of the lack of evidence about the use of antibiotic prophylaxis in hepatic surgery, it is routinely used in clinical practice and is recommended in the guidelines by inferring from evidence in biliary surgery.[331] The antibiotics used in most of the studies were first- and second-generation cephalosporins, or ampicillin-sulbactam.

In their clinical trial in patients undergoing hepatectomy with extrahepatic bile duct resection (excluding hepatopancreatoduodenectomy), Sugawara *et al*[413] based selection of antibiotics on preoperative bile cultures. When these were negative, first and second-generation cephalosporins were preferentially used; when they were positive, prophylaxis was adjusted to the microbiology of surveillance bile cultures (70% were gram-positive cocci, 60% of which were enterococci). In a retrospective review of 565 patients who underwent hepatectomy with extrahepatic resection of the biliary duct after preoperative biliary drainage, the same authors found that patients with positive bile drainage cultures had significantly more episodes of cholangitis with bacteremia.[414] Prophylactic antibiotics were based on previous culture results, as in the previous trial, and duration was according to the surgeon's discretion. There were no significant differences in the percentage of infectious complications. Once again, the microbes most often isolated in biliary drainage were *Enterococcus* spp, followed by *Klebsiella* spp, *Staphylococcus* spp and *Enterobacter* spp, which were also those most frequently isolated in patients with infection. [414] The only independent risk factor associated with postoperative infection caused by a multidrug-resistant pathogen was having an positive preoperative bile culture with the same multidrug-resistant isolate.[414]

In summary, there is no evidence for the use of antibiotic prophylaxis in simple hepatectomy. In major hepatectomy with extrahepatic bile duct resection, prophylaxis would be recommended. There are no specific studies on this type of surgery comparing single-dose prophylaxis with other durations, and recommendations should be inferred from the evidence in other surgeries. The rate of SSI in this surgery has not decreased, even with increased duration of prophylaxis. The recommended duration is one preoperative dose. In protracted surgery of this kind, redosing every 3 hours is important (depending on the half-life of the antibiotic used). When bile cultures are negative and there are no risk factors, a first- or second-generation cephalosporin is recommended, or amoxicillin-clavulanic acid if there are risk factors, given the very high rate of enterococci isolated. If there are previous cultures, prophylaxis should be adjusted to these.

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in simple hepatectomy* **(D-I)**
- *Recommended in major hepatectomy (includes extrahepatic biliary resection)* **(A-II)**.

Antimicrobial: *cefazolin* **(A-I)** *or amoxicillin-clavulanic acid* **(A-III)**

In case of previous bile cultures: adjust according to sensitivity **(A-II)**.

Beta-lactam allergy: *vancomycin plus gentamicin* **(A-III)**

Duration: *≤ 24 h* **(A-I)**, *possibly a single dose is enough* **(A-II).**

5.17.3. Pancreatic surgery

The average duration of surgery for pancreaticoduodenectomy is 5.5 hours and average blood loss is 350ml.[415] The rate of SSIs is 20-30%.[416] The main organisms causing infection are enterococci, as well as staphylococci, streptococci and gram-negative bacilli. Risk factors associated with SSIs are ASA ≥3, preoperative biliary drainage, prolonged surgery, concomitant surgery and significant intraoperative bleeding.[417]

Prophylaxis in pancreaticoduodenal surgery is indicated by inference from biliary surgery since there are no placebo-controlled comparative studies. In clean surgery (distal pancreatectomy), cefazolin is recommended; in the rest, second- and third-generation cephalosporins have been used or amoxicillin-clavulanic acid.[151,416,418,419] When there are previous bile cultures, antibiotic treatment may be adjusted to drug susceptibility patterns of the isolated organisms.[413,420,421]

When surgery is prolonged or there is massive blood loss, perioperative redosing is necessary. There is no evidence to support 48-hour antibiotic prophylaxis compared to less than 24 hours.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in pancreatic surgery* **(A-II)**

Antimicrobial:

- *Low-risk surgery (no bile duct manipulation): cefazolin* **(A-I)** *or amoxicillin-clavulanic acid* **(A-III)***. Add gentamicin in case of high prevalence of resistant GNB* **(B-III)***.*
- *High-risk surgery with bile microbiological information: adjust to previous microbiology* **(A-II)***.*
- *High-risk surgery without bile microbiological information: amoxicillin-clavulanic acid plus gentamicin* **(B-III)***.*

Beta-lactam allergy: *vancomycin plus gentamicin* **(B-III)***.*

Duration: *≤ 24 h* **(A-I)***, possibly a single dose is enough* **(A-II)***.*

5.18. Advanced peritoneal surgery, peritonectomy

Search terms: "Antibiotic prophylaxis" AND "Peritoneal cytoreductive surgery" OR "Peritonectomy".

The surgical procedures performed in radical treatment of peritoneal carcinomatosis depend on the primary malignancy and extent of the tumor. The procedures may include splenectomy, pancreatectomy, cholecystectomy, appendicectomy, lymphadenectomy and visceral, gastrointestinal or colorectal resection. It is often associated with hyperthermic intraoperative peritoneal chemotherapy (HIPEC), and sometimes early postoperative intraperitoneal chemotherapy (EPIC) via a catheter placed in the abdominal cavity.[422]

Given this scenario, the risk factors associated with SSI are numerous. Apart from patient-related factors (age, comorbidities, immunosuppression, tumor, malnutrition), there are those that are procedure-related and exogenous factors (length of procedure, surgical trauma, high-voltage electrosurgery, intraabdominal catheters, thoracic and abdominal drainage, intraperitoneal chemotherapy, high fluid therapy, blood transfusion, hospital stay).[422]

The most frequently isolated organisms are Enterobacteriaceae, predominantly *Escherichia coli*, *Enterococcus* spp., *Staphylococcus* spp., *Streptococcus* spp., *Bacteroides* spp., *Clostridium* spp. and sometimes *Candida* spp.[422–424]

There are no prospective studies, although administration of an antibiotic with anti-anaerobic activity is recommended. Amoxicillin-clavulanic acid would be a better choice than cefazolin alone, except when associated with metronidazole.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in advanced peritoneal cancer surgery* **(A-II)**

Antimicrobial: *cefazolin plus metronidazole or amoxicillin-clavulanic acid* **(A-III)***. Add gentamicin in case of risk of resistant GNB SSI* **(B-III).**

Beta-lactam allergy: *metronidazole plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-II)**

5.19. Urological surgery

Search terms: "Antimicrobial prophylaxis" AND "Urological surgery".

Urological surgery, open and laparoscopic, is classed as a clean-contaminated surgery[10] and antibiotic prophylaxis is recommended.[9] Simple cystoscopy and extracorporeal shock-wave lithotripsy are invasive procedures that do not require prophylaxis, except where there is some specific risk factor. The recommendation of prophylaxis in open or laparoscopic procedures such as nephrectomy is based on the general recommendation for prophylaxis depending on the degree of contamination.

Apart from the degree of contamination of the surgical wound, the reported risk factors for surgical site infection and urinary tract infection (UTI) after surgery and urological procedures include anatomic anomalies of the urinary tract, urinary obstruction, urinary stone, urethral or external catheters. [58] Preoperative UTI is one of the main risk factors for post-surgical infection. Other procedure-specific factors that have been reported include duration of postoperative catheterization, mode of irrigation (closed versus open) and postoperative pyuria.[58] The American Urological Association (AUA)[425] considers that certain host conditions (Table 7) may affect the response to infection and recommends antibiotic prophylaxis in some procedures where it is not normally indicated.

The organisms most commonly isolated in urinary infections are gram-negative bacilli, fundamentally *E. coli*, but also enterococci. In procedures where a skin incision will be made, regardless of whether or not it involves the urinary tract, there is also the possibility of *S. aureus* infection, coagulase-negative staphylococci and streptococci species, with *S. epidermidis* and *P. aeruginosa* if there is prosthesis

- Advanced age
- Anatomic anomalies of the urinary tract
- Poor nutritional status
- Smoking
- Long-term use of corticosteroids
- Immunodeficiency
- External catheters
- Colonized endogenous or exogeneous prosthetic material
- Distant coexistent infection
- Prolonged hospitalization

5.19.1. Simple cystoscopy (without manipulation)

<u>Search terms</u>: "Antimicrobial prophylaxis" AND "Urethrocystoscopy" OR "Urodynamic study" OR "Urethrocystography".

Use of prophylactic antibiotics for flexible cystoscopy is a controversial subject. Randomized studies and meta-analyses tend to use antibiotic prophylaxis to reduce post-procedural bacteriuria,[426–428] but the NNT to obtain a benefit is high.[428] Some clinical practice guidelines (Canadian Urological Association)[429] recommend antibiotic prophylaxis in high-risk patients (Table 7).

Other prospective studies[430–433] and controlled clinical trials[434–438] have not shown the benefits of antibiotic prophylaxis for these procedures.

Different antibiotics have been used in the studies mentioned, yet there are no comparative studies. When antibiotic prophylaxis is necessary, use of fluoroquinolones and trimethoprim-sulfamethoxazole is discouraged, because of the very high rate of *E. coli* resistance in our setting. Second-generation cephalosporins, amoxicillin-clavulanic acid or fosfomycin trometamol could be used in a single preoperative dose. If fosfomycin is used, it should be administered at least 3 hours before the procedure.

There is no evidence on prophylaxis before urodynamic testing, but by inferring from cystoscopy, it would not be recommended.

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in simple cystoscopy or urodynamics without risk factors* **(D-I)**.
- *Recommended in case of risk factors* **(B-III)**

Antimicrobial: *fosfomycin trometamol or cefuroxime or amoxicillin-clavulanic acid* **(A-II)**

Beta-lactam allergy: *Fosfomycin trometamol* **(A-II)**

Duration: *single preoperative dose* **(A-I)**

5.19.2. Transurethral resection of the prostate.

<u>Search terms</u>: "Antimicrobial prophylaxis" AND "Transurethral prostatic resection".

Transurethral resection of the prostate is classified as clean-contaminated surgery. Randomized studies recommend antibiotic prophylaxis for all patients who undergo this procedure.[439–442] Most of these studies were carried out with quinolones and co-trimoxazole, which are discouraged nowadays because of high rates of resistance. In a recent review of 9 clinical studies evaluating fosfomycin trometamol as antibiotic prophylaxis (3 g before and 24 hours after), 8 showed that it was effective in the prevention of urinary infection.[443] A systematic review of the literature comparing combined drugs with single antibiotic prophylaxis (8 studies) found that there were fewer infections with combination prophylaxis, all the regimens used ciprofloxacin, combined in most cases with an aminoglycoside.[444]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in transurethral prostate resection* **(A-I)**

Antimicrobial: *fosfomycin trometamol* **(A-II)** *or cefuroxime or amoxicillin-clavulanic acid (***A-III)**.

Beta-lactam allergy: *Fosfomycin trometamol* **(A-II)** *or gentamicin* **(A-III)**

Duration: *single preoperative dose* **(A-I)**

5.19.3. Transurethral resection of bladder tumor

Search terms: *"Antimicrobial prophylaxis" AND "Transurethral resection of bladder tumor".*

There are no conclusive data on the usefulness of antibiotic prophylaxis in transurethral resection of bladder tumors.[445–447] Some guidelines suggest administration of antibiotic prophylaxis if there are risk factors (table 7) or large tumors.[9,429]

> ***Recommendations for antimicrobial prophylaxis***
>
> ***Indication:***
>
> - *Not recommended in transurethral resection of bladder tumor* **(D-III)**
> - *Recommended in case of risk factors or large tumors* **(B-III)**
>
> ***Antimicrobial:*** *fosfomycin trometamol* **(A-II)** *or cefuroxime or amoxicillin-clavulanic acid* **(A-III)**.
>
> ***Beta-lactam allergy:*** *Fosfomycin trometamol* **(A-II)** *or gentamicin* **(A-III)**
>
> ***Duration:*** *single preoperative dose* **(A-I)**

5.19.4. Ureteral stent placement/removal. Outpatient endourologic surgery.

Search terms: *"Antimicrobial prophylaxis" AND "Cystoscopic stent removal" OR "Outpatient endourologic surgery".*

There are no conclusive studies in favor of routine use of antibiotic prophylaxis.[448,449] Administration of prophylaxis is indicated in patients with risk factors (Table 7).

> ***Recommendations for antimicrobial prophylaxis***
>
> ***Indication:*** *Recommended in ureteral stent insertion or removal and ambulatory endourological surgery in patients with risk factors* **(B-III)**
>
> ***Antimicrobial:*** *fosfomycin trometamol* **(A-II)** *or cefuroxime or amoxicillin-clavulanic acid* **(A-III)**
>
> *In patients with previous infection or catheter colonization, antibiotic prophylaxis should be adapted, based on previous urine cultures* **(B-II).**
>
> ***Beta-lactam allergy:*** *fosfomycin trometamol* **(A-II)** *or gentamicin* **(A-III)**
>
> ***Duration:*** *single preoperative dose* **(A-I)**

5.19.5. Ureteroscopic stone removal

Search terms: *"Antimicrobial prophylaxis" AND "Ureteroscopic stone removal" OR "Endoscopic extraction of upper urinary tract stones".*

The available studies are not conclusive.[450–453] Two recent meta-analyses concluded that preoperative antibiotic prophylaxis does not lower the risk of UTI, but that a single dose does reduce the incidence of pyuria and bacteriuria.[454,455] The efficacy of different antibiotic regimens could not be assessed. A single dose seems to be sufficient.[454,456]

Some guidelines suggest that administration of prophylaxis for ureteroscopic stone removal should be restricted to uncomplicated urolithiasis in patients with risk factors (Table 7) or patients with complicated or impacted urolithiasis.[429,457] Other guidelines recommend antibiotic prophylaxis in all patients when there is manipulation of the urinary tract and stone removal.[116]

> ***Recommendations for antimicrobial prophylaxis***
>
> ***Indication:*** *Recommended in ureteroscopic stone removal* **(C-III)**, *mainly in patients with risk factors* **(B-III)**.
>
> ***Antimicrobial:*** *fosfomycin trometamol* **(A-II)**, *cefuroxime or amoxicillin-clavulanic acid* **(A-III).**
>
> *In patients with previous infection or catheter colonization, antibiotic prophylaxis should be adapted, based on previous urine cultures* **(B-II).**
>
> ***Beta-lactam allergy:*** *fosfomycin trometamol* **(A-II)** *or gentamicin* **(A-III).**
>
> ***Duration:*** *single preoperative dose* **(A-I)**

5.19.6. Extracorporeal shock wave lithotripsy

Search terms: *"Antimicrobial prophylaxis" AND "Extracorporeal shock wave lithotripsy".*

Controlled clinical trials,[458,459] prospective studies[460] and meta-analyses[461] have shown that, if the urine has been proven sterile beforehand, antibiotic prophylaxis is not necessary to prevent infections after extracorporeal shock wave lithotripsy (ESWL). Antibiotic prophylaxis may be indicated exclusively in patients with risk factors (Table 7).

Recommendations for antimicrobial prophylaxis

Indication:

- *Not recommended in ESWL if there are no risk factors* **(D-I)**
- *Recommended in ESWL in patients with risk factors* **(B-III)**

Antimicrobial: *fosfomycin trometamol* **(A-II)***, cefuroxime or amoxicillin-clavulanic acid* **(A-III)**

In patients with previous infection or catheter colonization, antibiotic prophylaxis should be adapted, based on previous urine cultures **(B-II)***.*

Beta-lactam allergy: *fosfomycin trometamol* **(A-II)** *or gentamicin* **(A-III)**

Duration: *single preoperative dose* **(A-I)**

5.19.7. Open or laparoscopic nephrectomy

<u>Search terms</u>*: "Antimicrobial prophylaxis" AND "Transperitoneal nephrectomy" OR "Laparoscopic nephrectomy".*

Open or laparoscopic transabdominal nephrectomy is classified as clean surgery, although depending on the reason for the surgery, it may be treated as clean-contaminated. This applies to patients undergoing kidney biopsy or percutaneous drain placement. There are no high-quality randomized studies,[462,463] and most are cohort studies.[464–467] Using the evidence available, prophylaxis is not recommended, except in high-risk patients.

Recommendations for antimicrobial prophylaxis

Indication: *Not recommended in open or laparoscopic nephrectomy* **(D-II)***, except if it is considered a clean-contaminated surgery or in high-risk patients* **(B-II)***.*

Antimicrobial: *cefuroxime or amoxicillin-clavulanic acid* **(A-III).**

In patients with previous infection or catheter colonization, antibiotic prophylaxis should be adapted, based on previous urine cultures **(B-II)***.*

Beta-lactam allergy: *gentamicin* **(A-III)**

Duration: *single preoperative dose* **(A-I)**

5.19.8. Percutaneous nephrolithotomy.

<u>Search terms</u>*: "Antimicrobial prophylaxis" AND "Percutaneous nephrolithotomy" OR "Percutaneous surgical interventions in patients with urolithiasis".*

Percutaneous nephrolithotomy with sterile urine is a clean-contaminated procedure and antibiotic prophylaxis is recommended. The most common organism is *E. coli*. Administration of antibiotic prophylaxis to patients with previous negative urine cultures led to a significant decrease in the frequency of infectious complications.[468–472] A single dose given before induction of anesthesia is sufficient.[469,473,474] No antibiotic has been shown to be better than any other;[473,475] antibiotic type should be adapted to local susceptibility patterns.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in percutaneous nephrolithotomy* **(A-II)**

Antimicrobial: *cefuroxime or amoxicillin-clavulanic acid* **(A-II)**

In patients with a history of UTI by ESBL-producing bacteria, antibiotic prophylaxis must be adapted **(A-III)**

Beta-lactam allergy: *gentamicin* **(A-III)**

Duration: *single preoperative dose* **(A-I)**

5.19.9. Simple prostatectomy (abdominal and laparoscopic)

<u>Search terms</u>*: "Antimicrobial prophylaxis" AND "Laparoscopic radical prostatectomy" OR "Radical retropubic prostatectomy".*

Abdominal or laparoscopic prostatectomy is clean-contaminated surgery that does not penetrate the digestive tract. Antibiotic prophylaxis reduces the rate of bacteriuria and urological sepsis after abdominal and laparoscopic prostatectomy.[476] A preoperative dose of antibiotic prevents infection.[476–480] The type of antibiotic should be adapted to local drug susceptibility patterns and antimicrobial stewardship programs designed to optimize antimicrobial use in the center.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in simple prostatectomy (abdominal and laparoscopic)* **(A-II)**

Antimicrobial: *cefuroxime or amoxicillin-clavulanic acid* **(A-III)**

Beta-lactam allergy: *gentamicin plus vancomycin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.19.10. Radical cystectomy with entry into the intestinal tract. Urinary diversion.

Search terms: "Antimicrobial prophylaxis" AND "Radical cystectomy".

There are no randomized studies of use of prophylaxis in cystectomy surgery with urinary diversion and neobladder construction with intestinal resection. This surgical procedure with intestinal resection is considered clean-contaminated and has a high rate of postoperative infection. Observational studies and others carried out in the setting of colorectal surgery confirm that administration of antibiotics with aerobic/anaerobic coverage is beneficial.[481–483] A randomized prospective study showed that a single dose was as effective as a 3-day dose.[484]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in radical cystectomy with entry into the intestinal tract and urinary diversions* **(A-II)**

Antimicrobial: *cefuroxime plus metronidazole or amoxicillin-clavulanic acid* **(A-II)** *(add gentamicin in case of high prevalence of resistant GNB)* **(B-III)**

Beta-lactam allergy: *gentamicin plus metronidazole* **(B-III)**

Duration: *single preoperative dose* **(A-II)**

5.19.11. Transrectal prostate biopsy

Search terms: "Antimicrobial prophylaxis" AND "Prostate Biopsy" OR "Transrectal prostate biopsy".

Two meta-analyses of randomized trials have shown the effectiveness of antibiotic prophylaxis versus placebo in the prevention of infectious complications after transrectal prostate biopsy.[442,485] Although prophylaxis of one day or more was initially used,[442,486] recent studies have demonstrated that a preoperative dose is just as effective as more prolonged antibiotic prophylaxis,[485,487] and that oral administration is as effective as intravenous or intramuscular delivery. Different classes of antibiotics have been compared (fluoroquinolones, co-trimoxazole, cephalosporins, amoxicillin-clavulanic acid and piperacillin-tazobactam among others) without finding one of them to be superior to the rest.[485] There is most evidence about fluoroquinolones and most guidelines recommend prophylaxis with fluoroquinolones or co-trimoxazole. They are not recommended as prophylaxis in our environment owing to the emergence of bacterial resistance to these antimicrobials. Fosfomycin trometamol administered 1–4 hours before biopsy achieves sufficiently high plasma concentrations to provide more than 90% population coverage against organisms with MIC ≤4 mg/L.[488] A systematic review of 5 studies comparing oral fosfomycin trometamol versus ciprofloxacin in transrectal biopsy prophylaxis found a lower rate of UTIs and significantly lower resistance rates in the fosfomycin group.[489] In fact, a recent meta-analysis of 15 studies (8 retrospective and 7 prospective) with 12,320 patients showed that targeted prophylaxis based on rectal smear culture results to rule out fluoroquinolone resistance versus empiric prophylaxis significantly reduced infectious complications (3.4% vs 0.8%, NNT was 39 in the targeted prophylaxis group).[490] In our environment therefore a single dose of fosfomycin trometamol, a dose of second generation oral cephalosporin or amoxicillin-clavulanic acid is preferred. Prophylaxis should be adjusted to local epidemiology. Owing to the high resistance rates, targeted prophylaxis is advisable, based on the results of a previous rectal smear.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in transrectal prostate biopsy* **(A-I)**

Antimicrobial:

- *Fosfomycin trometamol* **(A-I)** *or cefuroxime or amoxicillin-clavulanic acid, orally before the procedure* **(A-II)** *(add gentamicin in case of high prevalence of resistant GNB)* **(B-III)**.
- *If there is a history of UTI by multiresistant microorganisms, targeted prophylaxis is recommended* **(A-II)**.

Beta-lactam allergy: *fosfomycin trometamol* **(A-I)** *or gentamicin* **(A-III)**

Duration: *single dose 1-3 hours before the procedure* **(A-I)**

5.19.12. Clean surgery: testicular surgery, phimosis and other penile surgery without penile prosthesis implantation; open renal biopsy.

<u>Search terms</u>: *"Antimicrobial prophylaxis" AND "Scrotal surgery" OR "Vasectomy" OR "Varicocele surgery" OR "Phimosis".*

As in other previously mentioned procedures classed as clean surgery, antibiotic prophylaxis does not reduce the infection rates.[58,457,491]

Recommendations for antimicrobial prophylaxis

Indication: *Not recommended in clean surgery (testicular, phimosis and other penile surgeries without prosthetic implantation, and open renal biopsy)* **(D-II).**

5.19.13. Penile prosthesis

<u>Search terms</u>: *"Antimicrobial prophylaxis" AND "Penile prosthesis implantation".*

Since there are no randomized or comparative studies, the evidence for prophylaxis in this procedure is based on placement of prosthetic material in other procedures, such as orthopedic surgery.[151,457] A duration of 24 hours or less seems to be the most appropriate.[492–495]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in penile prosthesis implantation* **(A-III)**

Antimicrobial: *First- or second-generation cephalosporin* **(A-III)**

Beta-lactam allergy: *gentamicin plus vancomycin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.20. Gynecological surgery

5.20.1. Cesarean section

<u>Search terms</u>: *"Antimicrobial prophylaxis" AND "Cesarean delivery" OR "Cesarean section".*

Although some randomized, placebo-controlled clinical trials have questioned the efficacy of using antibiotic prophylaxis in low-risk cesarean deliveries,[496–498] multiple studies and meta-analyses have demonstrated its effectiveness.[499–503] There is sufficient evidence to recommend antibiotic prophylaxis in urgent and elective cesarean deliveries.[9,504,505]

The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) recommend the use of first-generation cephalosporins for their efficacy, spectrum of activity and low cost.[505,12] This recommendation is based on a meta-analysis of 51 randomized clinical trials that compared at least two antibiotic regimens and concluded that ampicillin and first-generation cephalosporins had similar efficacy.[506] More recent randomized clinical trials have shown a reduced frequency of infection by broadening the antibiotic spectrum, especially against *U. urealyticum* and *Mycoplasma*, by adding metronidazole, azithromycin or doxycycline to the standard prophylaxis.[507–511] A recent clinical trial in non-elective cesarean delivery[509] showed a significant reduction in the rates of SSI, especially of endometritis, when adjunctive azithromycin was added to cefazolin before incision. Azithromycin could play a role in urgent cesareans, especially in women with colonization or subclinical infection with chlamydia or *Mycoplasm genitalium*. More studies are needed to implement this strategy.

Historically, antibiotic prophylaxis in cesarean deliveries has been delivered after cord clamping[506,512,513] so as not to modify the bacterial flora of the neonate and to avoid masking possible neonatal sepsis. Nevertheless, several studies and meta-analyses, as well as CDC and WHO guidelines support administering prophylaxis before surgical incision.[1,2,512–514]

With respect to duration of antibiotic prophylaxis, various studies have shown that a single dose before surgery is not inferior to multiple doses after surgery for the prevention of postcesarean infections.[515–517]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in elective and urgent cesarean sections* **(A-I)**

Antimicrobial:

- *For elective caesarean section: cefazolin* **(A-I)***.*
- *For urgent cesarean section: cefazolin plus azithromycin* **(A-I)***.*

Beta-lactam allergy: *clindamycin plus gentamicin* **(B-III)**

Duration: *single dose before the incision* **(A-I)**

5.20.2. Hysterectomy

<u>Search terms</u>: *"Antimicrobial prophylaxis" AND "Hysterectomy".*

Hysterectomy, by both the vaginal and abdominal approach, is regarded as clean-contaminated surgery,[518] and preoperative prophylaxis is required.[519–521] Various meta-analyses have demonstrated the efficacy of first- and second-generation cephalosporins, [522–524] principally cefazolin and cefoxitin. There are no placebo-controlled studies for the effectiveness of prophylaxis in laparoscopic hysterectomy.

The most widely recommended regimen is single-dose cefazolin. Alternatives to cefazolin would be cefoxitin, cefuroxime or amoxicillin-clavulanic acid.[525,526] Studies that have compared different cephalosporin antibiotics showed that first-generation cephalosporins (mainly cefazolin) were equivalent to second- and third-generation cephalosporins in vaginal hysterectomy.[527–536] In abdominal hysterectomy, no objective differences have been found with respect to SSI rates after comparing second- and third-generation cephalosporins,[533,536–540] and cefazolin was non-inferior to second- and third-generation cephalosporins.[528,541–543] Even so, a randomized double-blind clinical trial in 511 vaginal hysterectomies noted a greater number of SSI in patients who received cefazolin rather than cefotetan.[544]

There is no evidence that a multidose strategy of antibiotic prophylaxis reduces the rate of surgical wound infections, urinary infections, febrile episodes or hospital stay compared to a single-dose strategy.[545] Studies comparing a single dose of one antibiotic versus multiple doses of another antibiotic showed that both regimens are effective in reducing the rate of postoperative vaginal and abdominal hysterectomy infections.[536–541,546] Few studies have included single-dose cefazolin[525,529,546,547] or amoxicillin-clavulanic acid,[525,547] but those that have indicate that a single dose of antibiotic would be sufficient as prophylaxis in gynecological surgery.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in abdominal and vaginal hysterectomy* **(A-I)**

Antimicrobial: *cefazolin or cefoxitina or amoxicillin-clavulanic acid* **(A-I)**

Beta-lactam allergy: *clindamycin plus gentamicin* **(B-III)** *or vancomycin plus gentamicin* **(B-III)**

Duration: *single preoperative dose* **(A-I)**

5.20.3. Adnexectomy and tubal ligation

<u>Search terms</u>: *"Antimicrobial prophylaxis" AND "Adnexectomy" OR "Tubal ligation" OR "Tubal sterilization".*

Adnexectomy, or ovariectomy without hysterectomy, is considered a class I or clean surgery, with a low risk of infection. Antibiotic prophylaxis is not required.[548,549] Tubal sterilization or ligation, by laparoscopy or minilaparotomy is also clean surgery for which antibiotic prophylaxis is not required.[548–550]

Recommendations for antimicrobial prophylaxis

Indication: *Not recommended in adnexectomy and tubal ligation* **(D-III)**

5.20.4. Induced abortion and puerperal curettage

Search terms: *"Antimicrobial prophylaxis" AND "Abortion" OR "Uterine evacuation".*

In the context of legally induced abortion, the rates of upper genital tract infection are generally below 1%. The risk is higher if there is untreated gonococcal infection or chlamydia.[551] A meta-analysis of 17 clinical trials supports the use of antibiotic prophylaxis in surgical abortion in the first trimester.[552] There is less quality evidence in medical abortion; a rate of infection of 0.32% has been estimated based on 6 prospective studies. Given that the tendency with new oral treatments is towards a lower incidence, the number of patients needed to treat (NNT) to prevent one infection has been estimated at 5,000.[553]

The most effective placebo-controlled antibiotics studied have been nitroimidazole, beta-lactams and tetracyclines (RR 0.54, 95%CI 0.37-0.77; RR 0.46, 95%CI 0.27-0.80; and RR 0.37, 95%Ci 0.14-0.98, respectively). A single dose given preoperatively was as effective as treatment over several days.

In a clinical trial, the effectiveness of universal prophylaxis (1 g of metronidazole rectally plus doxycycline every 12 hours for seven days) was compared with a screen-and-treat policy in which women were screened first for *Chlamydia*, gonococcus and bacterial vaginosis;[554] those who tested positive received treatment for the diagnosed infection (doxycycline, ciprofloxacin and metronidazole, respectively) and were sent to follow-up appointments for couples, while those who tested negative did not receive treatment. Post-abortion genital infections were more frequent in those who tested positive (most did not attend the appointments). Prophylaxis may not be generalizable to the whole population and may be more effective in voluntary terminations of pregnancy than in therapeutic abortion.

There are no controlled studies on second-trimester abortions, but the same approach used for first-trimester abortions may be effective.

In the absence of new controlled studies, antibiotic prophylaxis is recommended for all surgical abortion procedures.

The approach that has been most studied and recommended is oral doxycycline taken on an empty stomach.[521] Metronidazole is an alternative,[521] although the efficacy of adding metronidazole in women with vaginosis is not fully demonstrated.[553] Azithromycin, 1 g in a single dose and given with metronidazole, may also be a reasonable alternative.[555]

Recommendations for antimicrobial prophylaxis

Indication:

- *Recommended for induced surgical abortion in the first trimester* **(A-I)***, the second trimester or puerperal curettage* **(A-III)***.*
- *Not recommended in medical abortion* **(D-III)***.*

Antimicrobial: *Doxycycline 100 mg orally 2 hours before or i.v. before the procedure* **(A-I)** *or azithromycin 1 g orally or i.v. plus metronidazole 500 mg orally* **(B-III)***.* ***Duration:*** *single preoperative dose* **(A-II)**

5.20.5. Postpartum vaginal tear repair (III/IV)

Search terms: *"Antimicrobial prophylaxis" AND "Perineal tears" OR "Postpartum".*

There is only one clinical trial in this surgery.[556] Nevertheless it is recommended to give antibiotic prophylaxis with a second-generation cephalosporin (cefoxitin) or amoxicillin-clavulanic acid for third- or fourth-degree postpartum vaginal tears (those affecting the anus and rectum, respectively.

Recommendations for antimicrobial prophylaxis

Indication:

Recommended in postpartum vaginal tear repair (III/IV) **(A-I)***.*

Antimicrobial: *cefoxitina or amoxicillin-clavulanic acid* **(A-I)***.*

Beta-lactam allergy: *clindamycin plus gentamicin* **(B-III)***.*

Duration: *single preoperative dose* **(A-I).**

5.21. Transplants

5.21.1. Kidney transplantation

<u>Search terms</u>: "Antimicrobial prophylaxis" AND "Kidney transplantation" OR "Renal transplant recipients".

Kidney transplantation is clean-contaminated surgery without entry into the digestive tract. It has been associated with a postoperative infection rate ranging from 10% to 56%, with the two most common types of infection being urinary tract infection (UTI) and SSIs. Infection-related morbidity associated with graft loss occurs in as many as 33% of cases, according to some studies. Mortality associated with postoperative infection in the kidney transplant recipient is considerable and ranges from 5 to 30%.[9]

With antibiotic prophylaxis, SSI in transplant recipients ranges from 5 to 30%. Most of the infections are superficial in nature and occur within the 30 days following transplantation. Risk factors for SSI in renal transplantation include contamination of organ perfusate, patient-specific factors such as diabetes, glomerulonephritis or obesity, as well as factors associated with the procedure, such as ureteral leakage, hematoma formation, immunosuppressive therapy and finally, postoperative complications such as acute graft rejection, reoperation and delayed graft function.[9] A significant difference in SSI rates after kidney transplantation has been noted in immunosuppression regimens that include mycophenolate mofetil versus sirolimus. Sirolimus is an independent risk factor for SSI.[9]

Surgical site infection in kidney transplant recipients is caused by gram-positive organisms, in particular *Staphylococcus* spp. (including *S. aureus* and *S. epidermidis*) and *Enterococcus* spp., gram-negative bacilli, especially *E. coli*, *Enterobacter* spp., *Klebsiella* spp., *Pseudomonas aeruginosa* and also yeast with *Candida* spp. Multidrug-resistant pathogens found include MRSA, methicillin-resistant coagulase-negative *Staphylococcus* and carbapenem-resistant *P. aeruginosa.* This resistance may be related to previous antibiotic treatment and the antibiotic used in prophylaxis for UTIs or *Pneumocystis jiroveci* pneumonia.[9]

Based on the studies of antibiotic prophylaxis in kidney graft recipients published so far, it is difficult to make recommendations.[557–563] A randomized controlled trial compared antimicrobial prophylaxis versus no prophylaxis and found benefits for the prevention of SSI in the prophylaxis group, although the study contained biases that limited the highest scientific recommendation.[558] Nevertheless, based on the literature available, routine use of systemic antimicrobial prophylaxis is justified in patients undergoing kidney transplantation. A number of studies have consistently shown that patients who receive antibiotic prophylaxis experience lower rates of postoperative infection than those who do not, both in living-related donor and cadaveric donor transplants.[9]

Another multicenter randomized controlled trial compared one-dose versus multiple-dose antibiotics and found no differences in SSI rates, although that study too had biases.[559] Cefazolin has been the most widely used antibiotic prophylaxis in kidney transplantation.[559,560] A randomized controlled study that evaluated whether or not it was necessary to use vancomycin as surgical prophylaxis showed that it did not appear to reduce infection caused by gram-positive bacteria, nor did it have an effect on colonization or infection with vancomycin-resistant *Enterococcus*.[561] In a retrospective study, amikacin was superior to cephalosporins in the prevention of surgical infection, although the main causative organisms of infection were ESBL-producing Enterobacteriaceae.[564]

There is no evidence on the need to switch prophylaxis when there is colonization with multidrug-resistant organisms or pre-transplant bacteriuria in the donor or the recipient. The risk of post-kidney transplant invasive candidiasis, unlike in the case of pancreas transplants, is too low to justify systematic prophylaxis.[565]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in kidney transplantation* **(A-II)**.

Antimicrobial: *cefazolin* **(A-II)**, *consider adding gentamicin if high prevalence of resistant GNB* **(B-III)**.

Beta-lactam allergy: *vancomycin ± gentamicin* **(B-III)**.

Duration: *single preoperative dose* **(A-II)**.

5.21.2. Pancreas – Simultaneous pancreas/kidney transplantation

<u>Search terms</u> "Antimicrobial prophylaxis" AND "Pancreatic transplantation" OR "Simultaneous OR combined pancreas-kidney transplantation".

Infectious complications are the leading cause of morbidity and mortality in patients undergoing pancreatic or simultaneous pancreas-kidney (SPK) transplants. The frequency of SSI is in the range of 7–50% in transplanted patients receiving antimicrobial prophylaxis. The majority occur within the first 30–90 days after transplantation. UTIs are also common during this period, with rates from

10.6% to 49% in pancreas transplant recipients who receive antibiotic prophylaxis. They are much more common in recipients with bladder drainage versus enteric drainage of exocrine secretions.[9]

Patients with pancreas or SPK transplants are at increased risk for SSI and other infections owing to the immunosuppressive effects of diabetes mellitus, combined with the immunosuppressive drugs used to prevent graft rejection. Other risk factors include prolonged surgery and ischemic times, organ donor age > 55 years, and enteric rather than bladder drainage of exocrine secretions. The organisms that cause deep SSI are generally gram-positive (*Enterococcus* spp., *Streptococcus* spp., *Peptostreptococcus* spp.) and gram-negative (*Enterobacter* spp., *Morganella* spp. and *B. fragilis*), although *Candida* spp. are also found. Anaerobic organisms are rarely involved.[9]

Only one clinical trial, controlled but not blinded, has evaluated antibiotic prophylaxis in pancreas transplantation, but there are none in SPK transplants. This trial, mentioned in the previous section on kidney transplantation, was primarily conducted on kidney transplant patients, although it also included 24 pancreas transplant patients; no differences in postoperative infection rates were found using vancomycin plus gentamicin compared with cefazolin plus gentamicin.[561] Other published studies are retrospective and found a decrease in the rates of SSI of 7%–50% using prophylaxis versus 7%–33% for historical controls.[561,566–572] Possible factors explaining the disparity in rates are variations in the definitions of SSI, antibiotic prophylaxis regimens, immunosuppression protocols and the surgical technique used. A wide variety of antibiotics have been used, but since these are frequently wound infections and cefazolin appears to be as effective as other regimens in observational studies, use of cefazolin is recommended.[9] Indeed, in a retrospective study[570] of pancreas and combined pancreas-kidney transplants using a single preoperative dose of cefazolin, the rates of superficial and deep SSI were 5% and 11%, respectively, which is worthy of note considering the high infection rates in later studies using broader-spectrum prophylaxis and longer duration, sometimes caused by fungal and multidrug- resistant organisms. This may in part have been due to prolonged prophylaxis and the inclusion of non-surgical site infections.

It is common practice in many centers to use broad-spectrum antibiotic prophylaxis, including antifungals and antivirals, in these types of transplant. Given the frequent colonization of the duodenum with *Candida* species and isolation in SSIs, it is usual to administer an antifungal in surgical prophylaxis. Reported risk factors for posttransplantation fungal infection include enteric drainage, vascular thrombosis and postreperfusion pancreatitis,[571]which are postoperative factors that are clearly difficult to predict beforehand anticipate before the surgery. In an observational study, prophylaxis with fluconazole did not significantly reduce SSI caused by *Candida* spp.,[571] although transplant rejection and mortality were more common in patients with fungal and bacterial infections compared with those with bacterial infection only.

In short there are no randomized controlled clinical trials specifically designed to evaluate the efficacy of antimicrobial prophylaxis in pancreas and simultaneous pancreas-kidney transplants, which prevents a recommendation based on the highest level of evidence. Nevertheless, the type of surgical procedure, the susceptibility of the host and extrapolation from the high strength of evidence available for antimicrobial prophylaxis in duodenal surgery[9,331] makes it possible to establish a recommendation. The recommended regimen is cefazolin, with clindamycin or vancomycin combined with an aminoglycoside (gentamicin) as reasonable alternatives for those with beta-lactam allergies. Duration of prophylaxis should be restricted to 24 hours or less. For patients with a high risk of *Candida* infection (enteric drainage, vascular thrombosis, reperfusion pancreatitis), fluconazole adjusted for renal function could be considered. Liposomal amphotericin B is preferable in centers with a high prevalence of non-albicans *Candida* species.[565]

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in pancreas and SPK transplantation* **(A-II).**

Antimicrobial: *Cefazolin* **(A-II)***, or amoxicillin-clavulanic acid* **(B-II)** *(due to the frequent implication of enterococci).*

Consider adding an aminoglycoside according to local epidemiology or if prior colonization with multidrug-resistant organisms **(B-III)**.

Consider adding fluconazole if there is a high risk of infection with Candida spp (enteric drainage, vascular thrombosis, pancreatitis after reperfusion) **(C-III)**.

Beta-lactam allergy: *vancomycin plus gentamicin* **(B-III).**

Duration: *single preoperative dose* **(A-II)***, additional intraoperative doses if surgery is prolonged or there is major blood loss* **(B-II)**.

5.21.3. Liver transplantation

<u>Search terms</u>: *"Antimicrobial prophylaxis" AND" Liver transplantation".*

More than 25,000 patients worldwide receive liver transplants every year.[573] This procedure is increasing with good results and one-year patient survival is above 80%. Prevention of infection is a very important objective in this patient group, which is particularly vulnerable to the development of perioperative infections due to the immunosuppressive effect, not only of the drugs, but also of cirrhosis, malnutrition, prolonged duration of surgery and transfusion of hemoderivatives. The overall incidence of infection after liver transplantation ranges between 53% and 79%, mostly within the first month following surgery[574]; between 10-37% of these are surgical wound infections and have been associated with graft loss and higher mortality.[575] In a Spanish prospective series of 1,222 patients who underwent liver transplantation, the incidence of SSI was 8.8% (accumulated incidence 10.3%).[576] Consequently, while no controlled prospective studies have evaluated the efficacy of antibiotic prophylaxis in this kind of surgery, it is routinely recommended. While some studies have questioned its efficacy, its use is nevertheless widespread. The quality of the evidence is also very variable.[577] There are currently no established recommendations on perioperative prophylaxis in solid-organ transplantation apart from the IDSA/ASHP/SIS/SHEA guidelines, although it is not used in many institutions in the United States.[9]

Many risk factors associated with post-liver transplantation infectious complications have been reported, both host-related (long hospital stay or ICU, use of antimicrobials in the preceding 3–4 months, diabetes mellitus (DM) and hemochromatosis, high prognostic category, ascites, obesity, previous liver surgery, previous liver or kidney transplantation); procedure-related (long surgery, entry into the gastrointestinal tract, Roux-en-Y anastomosis, transfusion of >4 units of red blood cells, anastomotic leakage); donor-related; or factors related to the transplant (rejection, need for dialysis, immunosuppressive drugs).[575,576,578]

The organisms that cause surgical site infection in liver transplantation are basically gram-negative bacilli (principally *Enterobacteria* species and more rarely species of *Acinetobacter* or *Pseudomonas*), followed by enterococci, *S. aureus* and coagulase-negative *Staphylococci* and *Candida* spp.[576,579,580] These patients have the highest rates of infection caused by multidrug-resistant organisms, especially vancomycin-resistant enterococci and ESBL-producing Enterobacteriaceae, which are fundamentally associated with antibiotic treatment prior to transplantation.[575]

As has been mentioned, no clinical trials have evaluated the efficacy of different types of antimicrobials and the observational studies that have been published generally compare broad-spectrum antimicrobials (amoxicillin-clavulanic acid, ampicillin-sulbactam, glycopeptide with third-generation cephalosporin) with first- and second-generation cephalosporins, with varying results. In their prospective series of 1,222 liver transplant patients, Asensio et al observed more than 8 antibiotic prophylaxis regimens, the most frequent being amoxicillin-clavulanic acid and combinations of glycopeptide with antipseudomonal penicillin or glycopeptide with aztreonam.[576] Cefazolin was associated with a higher risk for SSI, but not in the adjusted analysis. The authors recommend amoxicillin-clavulanic acid, or a third- generation cephalosporin combined with amoxicillin in centers with a low incidence of penicillin-resistant bacteria and vancomycin-resistant enterococci; vancomycin is suggested as prophylaxis in hospitals with a high prevalence of MRSA. They also suggest that performance of urine and stool cultures prior to transplantation may be useful for detecting multidrug-resistant enterococci, given that these are a serious problem in transplant units,[576] and possibly also for detecting other multidrug-resistant organisms. North American guidelines recommend a combination of third-generation cephalosporin and ampicillin or piperacillin-tazobactam, with a duration of less than 24 hours.[9] A recent review recommends ampicillin-sulbactam for no more than 48 hours. There is no evidence to support its use for more than 24 hours; the recommendation is made by inference from evidence in pancreatic and hepatobiliary surgery. After implementation of an antimicrobial stewardship intervention that included a series of preventive measures to reduce the incidence of SSIs in liver, kidney, pancreas, and simultaneous kidney-pancreas and intestinal transplants (shaving, preoperative shower and skin antisepsis, ventilation in the operating room, surgical scrubbing and use of gloves), and in the case of liver transplants, prophylaxis with ceftriaxone and vancomycin 30 minutes before surgery, Frenette et al. successfully reduced SSIs in those surgeries from 25% to 10.7% (a 58% reduction, p=0.005).[419]

It has been suggested that certain immunosuppressive agents would make the patient susceptible to certain infections, although Hadley et al. found no differences between tacrolimus and cyclosporin.[581]

Many centers use antifungal prophylaxis, although there are no studies to endorse its use. Risk factors associated with *Candida* species infections are prolonged surgery, excessive blood loss, pretransplant colonization, kidney failure requiring hemodialysis, and reoperation.[9,575,576] There is no evidence to support its use in patients with previous colonization. Surgical prophylaxis should not be confused with antifungal prophylaxis after transplantation. No clear benefits have been found for selective bowel decontamination or use of probiotics before transplantation. [9,575]

In summary, no high-quality comparative studies have evaluated the efficacy of prophylaxis in liver transplantation or the best antibiotics. The recommendations are based on observational studies and inferred from evidence in pancreatic and hepatobiliary surgery. There is no evidence to recommend antifungal prophylaxis, or duration of more than 24 hours. Coverage against enterococci should be considered when selecting prophylaxis, given the high prevalence of SSIs that are caused by these organisms.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in liver transplantation* **(A-II)**

Antimicrobial: *Amoxicillin-clavulanic acid* **(A-III)**. *Consider adding an aminoglycoside according to local epidemiology or prior colonization with multidrug-resistant microorganisms* **(B-III)**.

Individualize prophylaxis according to pre-transplant colonization or infection **(B-III)**.

Beta-lactam allergy: *vancomycin plus gentamicin* **(B-III)**.

Duration: *≤ 24 h* **(A-II)***, additional intraoperative doses if surgery is prolonged or there is significant blood loss* **(B-II)**.

5.21.4. Small bowel transplant

<u>Search terms</u>: *"Antimicrobial prophylaxis" AND "Intestinal transplantation".*

The incidence rate of SSIs following small bowel transplants is extremely high, between 14% and 53%, rising to 25.7–100% if a prosthetic mesh is used to close the abdomen. Risk factors for surgical infection are associated with age, previous transplant, previous hospitalization, need for a mesh, reoperations, enterocutaneous fistulas, need for skin flaps, radiation therapy and immunosuppressants.[575]

In this type of surgery, the SSIs are normally polymicrobial, with gram-negative bacilli predominating, especially Enterobacteriaceae and Pseudomonas species, followed by gram-positive cocci (enterococci and staphylococci*)*, although anaerobes and yeasts, especially *Candida* spp., are also common. Infections caused by multidrug-resistant organisms have been reported, such as ESBL-producing Enterobacteriaceae, *P. aeruginosa*, MRSA, and vancomycin-resistant enterococci, possibly associated with hospitalization and antibiotic treatment prior to the infection.

While antibiotic prophylaxis is standard practice, there are no specific studies and the guidelines do not provide recommendations for small bowel transplantation. Broad-spectrum antibiotic regimens have been used as prophylaxis, with combinations that provide coverage against gram-positives (including enterococci), gram-negatives (including *Pseudomonas*), anaerobes and fungal pathogens. Many patients have infections caused by the same organisms that were covered in prophylaxis, which suggests that antibiotic prophylaxis alone is not sufficient to prevent SSIs in these patients. There is no consensus about duration, with regimens of up to 72 hours being recommended. It may possibly be more appropriate to maintain optimal drug concentrations during surgery rather than extend duration of prophylaxis.

The prophylactic regimen will depend on previous cultures and previous risk factors for infection with multidrug-resistant organisms.[575]

Consequently, prophylaxis would be recommended by inferring from evidence in other types of transplant surgery and the high risk for postoperative infection. If there are no risk factors for MDRO infection, prophylaxis would be similar to that used in colon surgery: amoxicillin-clavulanic acid plus gentamicin, with vancomycin plus gentamicin plus metronidazole in cases of beta-lactam allergy. Prophylaxis should be adjusted according to previous microbiology. Consider adding fluconazole if there are risk factors for *Candida* spp. In this connection, the predictors of infection reported in the literature for critically ill surgery patients could be used here for prediction of *Candida* infection: colonization with *Candida* in at least three body sites on at least 2 consecutive screening days, or a colonization index >5 (calculated by dividing the number of positive sites by the number of cultured sites), or a previous *Candida* infection.[582] Pharynx, perineal and urine cultures have the highest positive predictive value (PPV), so that 3 positives at a single screening increases the PPV to 99–100%.[583] Duration of prophylaxis for more than 24 hours is not recommended. Perioperative redosing is advisable every 3 hours if there is excessive blood loss during the procedure.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in small bowel transplant* **(A-II)**.

Antimicrobial:

- *If there are no risk factors for infection with multidrug-resistant organisms: amoxicillin-clavulanic acid plus gentamicin* **(A-III)**.
- *Consider adjusting prophylaxis to previous microbiology, add fluconazole if there are risk factors for Candida spp* **(B-III).**

Beta-lactam allergy: *Vancomycin plus gentamicin plus metronidazole* **(B-III)**.

Duration: *≤ 24 hours* **(A-II)**, *consider additional intraoperative doses if surgery is prolonged or there is major blood loss* **(A-III)**.

5.21.5. Heart, lung and combined heart-lung transplantation

Search terms: "Antimicrobial prophylaxis" AND "Solid organ transplantation" AND "Heart transplantation" OR "Lung transplantation".

There are few well-designed comparative studies on preoperative antibiotic prophylaxis in heart, lung or heart-lung transplantation. In several studies, prophylaxis varies according to existing infections in the donor or recipient.[584]

Heart transplant: Infection remains a major complication, and is the cause of death in 14% of patients in the first year after transplantation.[585] The mean 10-year graft survival rate is 49%. Cardiothoracic procedures performed without prophylaxis have been associated with SSI rates ranging between 9% and 55%.[586] In patients who underwent heart transplantation and received prophylaxis, SSI rates were 5–9%.[587] Reported risk factors for infection after heart transplantation include: age, use of ciprofloxacin in prophylaxis, positive pacemaker cultures, BMI>30 kg/m^2, female, hemodynamic instability, or previous use of a ventricular assist device.[587] Other risk factors for infection include active infection in the donor, time from organ recovery to reperfusion, and the type of immunosuppressive regimen used. In addition, early post-operative infection after transplantation has been associated with higher rates of primary graft dysfunction.[588] The pathogens most frequently involved in these infections are gram-positives (fundamentally *Staphylococcus* species).[587] Other organisms that may also be involved include Enterobacteriaceae, *P. aeruginosa*, *Stenotrophomonas maltophilia* or *Candida* spp. The incidence of MRSA and vancomycin-resistant enterococci (VRE) depends on local epidemiology.

Despite the dearth of literature in this regard, it seems clear that prophylaxis is safe and effective in this setting.[584] In one study, the SSI rate among patients who received prophylaxis with cefotaxime and flucloxacillin was 4.5%.[589] First- and second-generation cephalosporins are considered just as effective and are the antibiotics of choice.[590] There is no consensus about the optimal duration of prophylaxis. Various studies have shown the usefulness of 24–48 hours of prophylaxis with cefazolin or vancomycin.[591] Vancomycin (with or without gentamicin) is a reasonable alternative in institutions where MRSA is highly prevalent (see point 4.5), in patients with MRSA colonization or who are allergic to beta-lactams. It may be necessary to use perioperative redosing if the procedure exceeds 3 hours or there is heavy loss of blood. Patients with an infection associated with an external ventricular assist device should receive prophylaxis with coverage against the organism involved in the infection. Patients requiring extra-corporeal membrane oxygenation (ECMO) before transplantation should be treated in the same way.

Lung and heart-lung transplantation: Mean survival at 10 years is 29% in double-lung, 17% in single-lung, and 26% in heart-lung transplantation.[585] Infection is the most common complication after lung and heart-lung transplantation and is in fact the leading cause of death in the first year after transplantation (24.8% in lung, and 18.3% in heart-lung).[585] The SSI rate was 13%, with the majority being organ/space infections (72%). The overall rate of mediastinitis in a similar cohort study was 2.7%.[592] Bronchial anastomotic infections (especially fungal infections) are potentially fatal in these patients.[593]

The most important risk factors for infection following transplantation are the degree of clinical deterioration at the time of the transplant, α-1 antitrypsin deficiency and retransplantation. Risk factors for the development of pneumonia include pre-operative colonization with gram-negative bacilli or previous colonization or infection in the donor. Predictors of mortality are cystic fibrosis, nosocomial infection and the need for mechanical ventilation before transplantation.[592] Risk factors for developing mediastinitis are the degree of immunosuppression, impaired renal function, previous sternotomy and reexplanation due to bleeding. We should bear in mind that the transplant alters mucociliary clearance and suppresses the cough reflex, which means that these patients are going to be at very high risk of developing pneumonia.[584]

The most important organisms in infection associated with lung transplantation are gram-negative bacilli and fungal pathogens, not forgetting that gram-positive cocci may be involved in mediastinitis cases. The organisms most commonly isolated in patients with SSIs are *P. aeruginosa*, *Candida* species, *S. aureus*, enterococci, *S. epidermidis*, *Burkholderia cepacia*, *E. coli* and *Klebsiella* species.[592] The lung donor plays a very important role in transmission of pathogens to the recipient. Almost 90% of bronchial washings obtained from the donor are positive for at least one organism. In turn, the recipient may also be the source of infection of the transplanted lung, as is the case of patients with cystic fibrosis, in whom the pathogens are frequently multidrug-resistant.

No randomized clinical trials have determined the most appropriate prophylaxis for this population, although prophylaxis in this setting is accepted as standard practice.[584] The objective of prophylaxis in these patients is to prevent SSIs as well as pneumonia. Indeed, in one study, use of prophylaxis reduced the frequency of post-transplant pneumonia from 35% to 10%.[594] First- and second-generation cephalosporins are the preferred antimicrobials. Even so, prophylaxis should be modified to provide coverage against any pathogen isolated in the respiratory tract of the donor or recipient. Patients with cystic fibrosis should receive prophylaxis based on previously isolated organisms (usually multidrug-resistant). Patients requiring ECMO as a bridge to transplantation with a history of colonization or infection should receive prophylaxis that includes coverage against the pathogens involved.

A number of antibiotic regimens have been used in studies including ceftazidime, floxacillin, tobramycin and itraconazole, as well as inhaled amphotericin B,[592] cefepime in patients without previous isolates[595] or metronidazole and aztreonam.[596] Antifungal prophylaxis should be considered when the donor or recipient lung cultures are positive for *Aspergillus* spp. or *Candida* spp.[597] With respect to duration of prophylaxis, there are studies that have evaluated 24–48 hours up to 14 days. In cases where prophylaxis was extended to 7–14 days, it was considered treatment for at-risk patients and not prophylaxis properly speaking.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in heart transplant* **(A-II)**.

Antimicrobial: *Cefazolin* **(A-II)**.

Patients diagnosed with an infection associated with a ventricular assist device about to have a heart transplant should receive prophylaxis that includes the organism involved **(B-III)**.

Beta-lactam allergy: *Vancomycin. Consider adding gentamicin according to local epidemiology and risk of GNB infection* **(B-III)**.

Duration: *single preoperative dose* **(A-II)**.

Recommendations for antimicrobial prophylaxis

Indication: *Recommended in combined heart-lung transplant* **(A-II)**.

Antimicrobial:

- *Cefazolin* ***(A-II).*** *This regimen should be modified in patients with previous cultures or positive donor cultures* ***(B-III)***.
- *Patients diagnosed with an infection associated with a ventricular assist device who are going to have a heart-lung transplant should receive prophylaxis that includes coverage against the organism involved* **(B-III)**.
- *Prophylaxis may sometimes include antifungals with activity against Candida spp. or Aspergillus spp. in certain patients (cystic fibrosis, donors or recipients colonized pre-transplant)* **(B-III).**

Beta-lactam allergy: *vancomycin, consider adding gentamicin according to local epidemiology and risk of GNB infection* **(B-III).**

Duration: *≤24 h* **(A-II)**. *Do not maintain prophylaxis until drainage is removed.*

If cystic fibrosis, treatment should be for at least 7 days, with coverage against pre-transplant organisms isolated **(B-II)**.

6. Conclusions

Antibiotic prophylaxis is one of the principal measures of preventing surgical infections. The objective is to achieve peak concentrations of the antibiotic in the relevant tissue before the start of surgery and maintain them throughout the procedure. In general, prophylaxis is recommended when there is a very high likelihood of postoperative infection, or when the consequences for the patient are potentially serious. It includes, at the very least, procedures classed as clean-contaminated, contaminated, and clean surgical procedures involving implantation of prosthetic material.

The antibiotics selected must be active against the organisms most frequently isolated in each type of surgical procedure and will usually be a first- or second-generation cephalosporin. The drugs should be administered intravenously at maximum therapeutic doses within the 120-minute interval before surgical incision, and modified for obese patients.

For most procedures, a single dose before the operation is recommended, which should never be continued beyond the first 24 hours after the operation. Perioperative redosing is more important than administering a postoperative dose when the wound is already closed and is indicated when the surgical procedure is more than twice the half-life of the antibiotic.

Any protocol for antibiotic prophylaxis should include recording compliance with its guidelines, an analysis of its results, and feedback of those results to members of surgical teams.

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