CONSENSUS DOCUMENT OF THE SPANISH SOCIETY OF INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY (SEIMC) AND THE SPANISH ASSOCIATION OF HEMATOLOGY AND HEMOTHERAPY (SEHH) ON THE MANAGEMENT OF FEBRILE NEUTROPENIA IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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SUMMARY

Febrile neutropenia is a common complication in patients with hematologic malignancies receiving chemotherapy and is associated with high morbidity and mortality. Infections caused by multidrug-resistant bacteria represent a therapeutic challenge in this patient population, since inadequate empirical treatment can seriously compromise prognosis. Also, reducing antimicrobial exposure is a cornerstone in the fight against resistance. The objective of these new guidelines is to update recommendations for the initial management of hematologic patients who develop febrile neutropenia in the present scenario of multidrug resistance. The two participating Societies (the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica and the Sociedad Española de Hematología y Hemoterapia), designated a panel of experts in the field to provide evidence-based recommendations in answer to common clinical questions. This document is primarily focused on bacterial infections. Other aspects related to opportunistic infections, such as other opportunistic infections, especially in hematopoietic stem cell transplantation, are also touched upon.

INTRODUCTION

Definition of febrile neutropenia (FN)

- The internationally accepted definition is that provided by the Infectious Diseases Society of America (IDSA),[1] and is identical to the National Comprehensive Cancer Network's (NCCN) definition.[2]
- Fever is defined as a single oral temperature measurement of ≥38.3Cº, or a temperature of ≥38Cº sustained over a 1-hour period.
- Neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC of <1000 cells/mm^3 that is expected to decline to below 500/mm^3 within 48 hours.

It is important to understand that the neutropenia grading scale used to discuss FN in this document is different from the ones considered for other types of patient. Neutropenia as such is an absolute decrease in ANC of more than 2 standard deviations below the normal population mean. In practice, neutropenia in adults is considered to be < 1800 neutrophils /mm^3.

The CTCAE (Common Terminology Criteria for Adverse Events) common toxicity criteria of the National Cancer Institute (NCI) of the United States classify neutropenia as follows: grade 1, ANC <1800 (lower limit of normality) to 1500/mm^3; grade 2, ANC <1500 to 1000/mm^3; grade 3, ANC <1000 to 500/mm;[3] and grade 4, ANC<500/mm^3.

For the definition of FN however, lower levels of neutropenia associated with a substantially increased risk of infection are considered. For risk of infection, an ANC <500/mm^3 (grade 4 neutropenia, CTCAE) and ANC <1000/m^3 expected to drop below 500/mm^3 (grade 3 neutropenia, CTACAE) are also taken into consideration. Patients with ANC <100/mm^3 present a higher risk than those with 100–<500/mm^3.

To calculate the ANC, the neutrophils and band cells are counted. Example: 700 leukocytes/mm^3 (65% segmented neutrophils, 10% band cells, 30% lymphocytes) = 455 S + 70 C = 525 ANC/mm^3.

The quantitative relationship between neutrophil count and risk of infection was established by Gerald Bodey in a 1966 study that included only 52 patients with acute leukemia.[3]

This is one of the most frequently cited articles in the history of medicine. The study showed that patients with ANC<100/mm^3 presented a very high (>50%) risk of infection, those with <500/mm^3 presented a 10-35% risk of infection, and those between 500 and1500/mm^3, a 10% risk. The number of severe infections with ANC >1000/mm^3 was low. Based on that study, it was established that the threshold for a very high risk of infection was ANC <500/mm^3, with a notably higher risk for ANC <100/mm^3.

The second point with practical implications is that the definition of fever is not adjusted to the way that temperature is taken in many hematology units. In Spain, it is not usual to take oral temperature, and instead axillary and, more recently, tympanic readings are used. The IDSA explicitly advises against taking axillary temperature since it may not faithfully reflect core temperature. In practice, for the consideration of fever, oral temperatures values are assimilated to axillary or ear temperatures. This is not exact, since the axillary temperature is generally lower than oral temperatures.

A diagnosis of FN has implications for treatment: it identifies which patients should receive immediate empirical antimicrobial therapy. The administration of antibiotics should be initiated promptly after presentation at the hospital or in the consulting room. ASCO guidelines recommend that the first dose of antibiotics should be administered urgently, within the first hour of seeing the patient.[4] This is very important and steps should be taken to ensure that it is carried out, particularly if the patient is not being managed in a hematology unit.

Early initiation of empirical antibiotic therapy is essential in patients with FN, since failure to do so can rapidly lead to a fatal outcome. Empirical therapy for FN has been established for many years in clinical hematology, although surprisingly, its efficacy has never been verified in a randomized controlled trial. It is based on the principle of risk management: weighing the toxicity of unnecessary treatment in some patients against the benefits of early treatment in others. This practice was established in 1971 after Schimpff published an uncontrolled study of 75 patients

with FN who were given empirical antibiotic therapy.[5] What now seems to us to be the natural course of action was contrary to orthodox antimicrobial treatment at the time, which was not to administer antibiotics until the causative agent had been identified (in this case, a positive blood culture). By using this empirical treatment, the mortality of patients with bacteremia due to *Pseudomonas aeruginosa* was successfully reduced to 7% at 72 hours, and to 30% at the final follow-up, which contrasted very favorably with the 50% and 91% rates respectively, obtained with the "orthodox" treatment until then.

Much has been learnt and many improvements have been made since Schimpff's time, and mortality due to bacterial infection in FN is currently relatively low (2-4%). The following sections of this document will review the diverse aspects of epidemiology, risk factors and management of this common complication. Nevertheless, the achievements made in the management of FN are threatened by the present-day increase in infections caused by multidrug-resistant bacteria, which constitute a growing cause of death.

Clinical characteristics of patients with FN

- In neutropenic patients, fever may be the only sign of infection.
- Neutropenia reduces or eliminates the signs of inflammation associated with infection, making diagnosis difficult.
- Neutropenic patients may have infection without fever, which can hamper or delay a correct diagnosis and treatment, with serious consequences.

Fever is common in patients with chemotherapy-induced neutropenia, and fluctuates from 10-50% in those with solid tumors to >80% in patients with hematologic malignancies receiving intensive chemotherapy.[1] The majority (60%) will not have either an obvious clinical focus of infection (20-30% of cases) or a positive culture (10-25% of cases, the most frequent

bacteremia), which means that managing the neutropenic patient with fever should be carried out rapidly and following a protocol, even when there is no other evidence of infection.

Signs and symptoms of focal inflammation are often muted or absent in neutropenia, which means that signs of infection during the physical exploration or in radiological or analytical tests are also minimized or eliminated. This may make it difficult to diagnose pneumonia, meningitis and urinary infection, among other infectious processes. As a result, the neutropenic patient may manifest only fever, yet have a severe infection at the same time.[1] In neutropenic patients, purulent sputum is found in only 8% of cases of bacterial pneumonia, and pyuria in 11% of urinary infections.[6] A patient with a lung infection can have a normal chest x-ray. This is particularly common in patients with a fungal infection in the lungs (most often aspergillosis) but also occurs in bacterial pneumonia.[6] A normal conventional chest x-ray in a patient with persistent fever, even when respiratory symptoms are absent, is not evidence of the absence of pulmonary involvement, but an indication for a pulmonary CT scan. In one classic study, a CT scan showed evidence of pneumonia in 60% of patients with febrile neutropenia whose chest x-rays were normal.[7]

Whereas the majority of patients with neutropenia and infection develop fever, infection can occasionally present without fever, particularly when the patient is receiving corticosteroid therapy. Findings such as cutaneous lesions, localized pain (typically perianal), hypotension, hyperventilation and signs of tissue hypoperfusion are suggestive of infection, even without fever. In such cases, also in the absence of fever, the neutropenic patient should be considered infected and empirical antibiotic therapy should be started immediately.

Epidemiological changes in the etiology of infectious complications in patients with FN

Bacteriology

1. Numerous studies have reported an increase in the percentage of gram-negative microorganisms recorded in the etiology of bacterial infections over the past 10 years. *Escherichia coli* is the most frequently isolated species, with a mean of 32.1%, followed by *P. aeruginosa* (20.1%), *Klebsiella* spp. (19.5%) and *Acinetobacter* spp. (8.2%). *Stenotrophomonas maltophilia* is considered an emerging pathogen and ranks fifth in isolates detected in cancer patients (3.7%).
2. In parallel, the global emergence of multidrug-resistant microorganisms has also been recorded. The three most commonly isolated pathogens in neutropenic patients (*E. coli, P. aeruginosa* and *Klebsiella pneumoniae*) can become resistant in more than 50% of cases to broad-spectrum cephalosporins, fluoroquinolones and aminoglycosides, even after removing fluoroquinolone prophylaxis from risk groups. The percentage of Enterobacteriaceae isolates producing CTX-M- or TEM-type extended-spectrum beta-lactamases (ESBLs) can be in excess of 35%, and carbapenem resistance in *Pseudomonas* spp. oscillates around 30%. Carbapenem resistance among Enterobacteriaceae is an emerging phenomenon and can fluctuate between 2% and 34%.
3. In consequence, increased failure of empirical therapy, mortality and higher hospital costs have been recorded.

Mycology

1. The incidence of invasive fungal infection in patients with neutropenia after hematopoietic stem cell transplantation (HSCT) is variable, and ranges from 1% in autologous HSC transplants to 7-12% in allogeneic transplants.
2. The most frequently isolated species isolated in candidemia in the neutropenic patient are non-*albicans Candida* species, with 70% of isolates in some studies, and *Candida*

tropicalis as one of the most common species (22%). In general, echinocandins continue to be active against the majority of Candida spp isolates, although resistance to this class of antifungals is starting to be observed in some institutions.

3. The most frequently identified species of filamentous fungi are *Aspergillus fumigatus*, *Aspergillus niger* and *Aspergillus flavus.* Although azole-resistant *Aspergillus* species have been detected in some centers, it does not at the present time constitute a clinical problem in our environment.

Summary of bacteriology

Numerous studies have recorded increased percentages of gram-negative microorganisms in the etiology of infectious complications in oncology and hematology patients in the past 10 years, both in general, and specifically during neutropenia. In spite of the heterogeneous nature of the studies in the selection of cases (only bacteremia versus any type of infection, different geographical areas, neutropenia also associated with solid cancer versus only hematologic malignancies), there has been a documented increase in the percentage of gram-negative isolates from 24.7% in 2007 to 75.8% in 2014, with a mean of 51.3%. In many studies, they were the most frequently isolated microorganisms. This figure varies from 48% (24.7-73.9%) if only isolates in blood cultures are counted, to 58.1% (54.4%-75.8%) if all samples are considered. [8–16] (Figure 1).

Various factors may account for this situation, including the following: use of *fluoroquinolone prophylaxis* in patients undergoing chemotherapy (CT) or HSCT, which would lead to alterations in the microbiota; the type or *intensity of the CT cycle* (myeloablative), since the most cytotoxic chemotherapy regimens would favor translocation; reducing and optimizing central venous catheter (CVC) usage would reduce infections caused by coagulase-negative staphylococci (CNS); a humid climate in certain countries favors *Pseudomonas* spp. infections;

the global emergence of multidrug resistance predisposes oncology and hematology patients to the acquisition of resistant strains. Finally, other risk factors predisposing to infection in general are associated with the progress of blood diseases (deterioration of the innate and adaptive immune response), splenectomy, graft-versus-host disease (GVHD) and its treatment, viral immunomodulation, the presence of concomitant infections and even genetic factors predisposing to pathogen recognition.[17,18]

An analysis of the frequency of isolates in clinical samples in these studies showed that *E. coli* was the most commonly isolated species, mean 32.1% (10.1%-53.6%), with a 30% frequency when studies with blood culture isolates were included, and 34% when all clinical samples were included.[9] *P. aeruginosa* was the second most common species isolated (20.1%), 18.8% in studies that only considered blood cultures and 22.7% in all clinical samples. The frequencies of *Klebsiella* spp. and *Acinetobacter* spp. were 19.5% (4.1%-44.6%) and 8.2% (0%-32%), respectively. The frequency of *Enterobacter* spp. isolates was 4.7% (2.2%-11.6%). Finally, the frequency of *S. Maltophilia* isolates was 3.7% (0%-16%), and is considered the fifth most commonly isolated pathogen in cancer patients.[9–19]

The global emergence of multidrug resistance has been reported as a parallel phenomenon. More than 50% of the isolates of the three most frequently isolated pathogens in neutropenic patients (*E. coli, P. aeruginosa* and *K. pneumoniae*) in these studies were resistant to cephalosporins, fluoroquinolones and aminoglycosides. The percentage of Enterobacteriaceae isolates with CTX-M or TEM-type ESBLs was above 35% and carbapenem resistance in *Pseudomonas* spp. fluctuated around 30%.[9,11,16] (Table1). The impact of antimicrobial prophylaxis on selection of multidrug-resistant microorganisms (MDROs) continues to be debated. Four studies analyzed the impact of quinolones on hematologic patients. In all them, the number of bacteremias without prophylaxis increased, with no impact on mortality, while in three of them, the isolation of MDROs increased after the use of quinolones.[12,20–22] Finally, in the last 4 years,

there has been an increase in carbapenem resistance in Enterobacteriaceae, which can fluctuate between 2% and 34% depending on the study,[16,23,24] and exceeds 50% in some centers in Italy.[25] A worse prognosis has been reported in these patients. More specifically, carbapenem resistance in bacteremias caused by *K. pneumoniae* has been identified as an independent risk factor for mortality in cancer and hematologic patients with neutropenia, along with septic shock, respiratory failure and inadequate empirical antimicrobial therapy.[16,18,19]

Summary of Mycology

The incidence of invasive fungal infection varies depending on the type of HSCT, whether autologous (1%) or allogeneic (7-12%), with aspergillosis being the most frequent. As a result of the diagnostic techniques available, selection of patients by risk group, and advances in antifungal prophylaxis and treatment, survival rates of more than 60% can be achieved at present.[27–29]

Non-*albicans Candida* species (*Candida tropicalis, Candida glabrata, Candida krusei, Candida parapsilosis*) are the most frequent isolates in patients with neutropenia (around 70% of isolates), with *C. tropicalis* being the most frequent (22%). Fifteen percent of neutropenic patients with candidemia develop a breakthrough infection. Possible causes include intestinal translocation in the context of mucositis, previous therapy with azoles with selection of non-susceptible strains (e.g. *C. krusei*), and not removing an infected central catheter, which perpetuates infection. Indeed, the continuing presence of a catheter and the situation of the underlying disease are the main predisposing factors for mortality in neutropenic patients with candidemia, which occurs in around 30% of cases. In general, echinocandins remain active against the majority of *Candida* spp. isolates, although some institutions are starting to observe resistance to this family of antifungals.[30–36] In the last two years, the global emergence of multidrug-resistant species such as *Candida auris* has been described.[37] Although this does not

currently represent a significant epidemiological change in the etiology of fungal infections in neutropenic patients, its possible development needs to be monitored.

For decades, invasive aspergillosis has been associated with high mortality rates, although there is also evidence that survival rates have improved in recent years, influenced by less toxic myeloablative conditioning regimens, using hematopoietic stem cells collected from peripheral blood, better methods of early detection, and more effective and better tolerated prophylactic regimens and antifungal treatment.[27,29] In these patients, the maximum risk of invasive aspergillosis occurs during neutropenia following remission induction chemotherapy and the development of GVHD and its treatment. The incidence is in the range of 1–7% and the most frequently identified species are *A. fumigatus*, *A. niger* and *A*. *flavus*. An improved prognosis for acute leukemia patients with invasive aspergillosis has been noted, as shown by an Italian group with a significant reduction in the attributable mortality rate from 48–60% to 27–32%.[38,39.] Likewise, with respect to the epidemiology of filamentous fungi, exceptional cases of infection due to cryptic species of azole-resistant *Aspergillus* spp. have been described in the past 5 years.[40] At present, these do not dictate any necessary changes in the diagnostic or therapeutic approach in patients with febrile neutropenia; nonetheless, the clinical impact of systemic prophylaxis with azoles in high-risk patients on the frequency or distribution of these species is unknown.

Figure 1. Cause of infections in onco-hematology patients. Bacteremia in patients with neutropenia.[9,11,16]

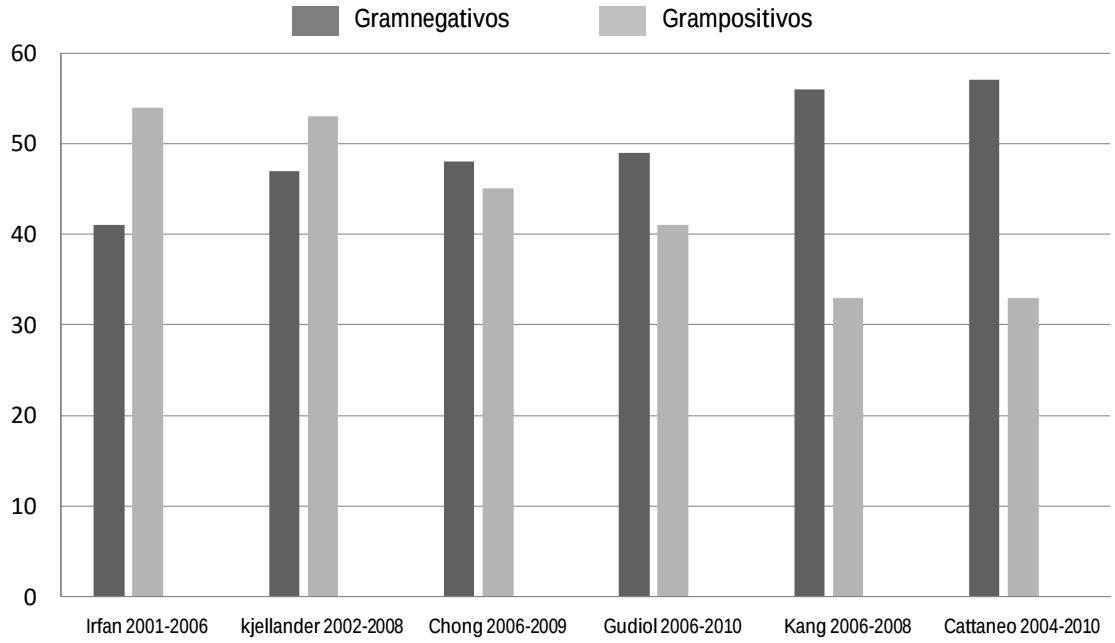


Table 1. Etiology and susceptibility of infections in onco-hematology patients with neutropenia, reported in 24 studies (2007–2014).

	Escherichia coli	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Acinetobacter* spp
Imipenem-meropenem	95% (90-100%)	98.5% (90-100%)	71% (24-100%)	61%-48%
Piperacillin-tazobactam	82% (87-100%)	71.8%	78% (61-100%)	53%
Cefepime	68% (18-100%)	68.7% (81-90%)	54%	42.6%
Ceftazidime	46.7% (15-94%)	54.7% (28.6-98.7%)	62%	64%
Amikacin	74% (7-99%)	80.3% (54.3-100%)	61.8%	54%
Ciprofloxacin	47.2% (14-66%)	61.1% (28.5-98.7%)	51.6%	58%
CTX-M or TEM-type ESBLs	35% (12-75%)	37.8% (3-66%)	-	-

11,651 isolates (5915 gram-negatives, from 24% to 75%, mean 51%).[9,11,16]

Justification and objectives.

Recent years have witnessed the re-emergence of bacterial infections with a gram-negative etiology in patients with febrile neutropenia (FN),[11] together with a significant increase in antimicrobial resistance, especially in gram-negatives.[41] These epidemiological changes are of particular importance in hematologic patients with FN because inadequate initial empirical antibiotic therapy can have a serious adverse effect on prognosis in high-risk patients. Likewise, the management of infections caused by multidrug-resistant bacteria is a major clinical problem in this population.

The management of hematologic patients has also changed in recent years, with a tendency towards outpatient care and new types of immunosuppressive treatment. In the era of multidrug resistance, the objective of these new guidelines is to update the recommendations for the initial management of hematologic patients who develop FN. This document focuses basically on bacterial infection. Other aspects associated with opportunistic infections, such as fungal infections or those due to other microorganisms, especially in hematopoietic stem cell transplantation (HSCT), are also touched upon. Only infections in adult patients will be discussed.

Methodology

The two participating Societies, the Spanish Society of Infectious Diseases and Clinical Microbiology (*Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica*) and the Spanish Association of Hematology and Hemotherapy (*Sociedad Española de Hematología y Hemoterapia)* nominated two coordinators for this project (CG and RC: an infectious diseases specialist and a hematologist). The coordinators selected the rest of the members of the panel of experts, which included infectious diseases specialists, microbiologists, hematologists and a pharmacologist. The scientific committees of both societies approved the proposal.

The present Document was written in accordance with the SEIMC guidelines for consensus documents (www.seimc.org), as well as the recommendations of the AGREE collaboration (www.agreecollaboration.org) for evaluating the methodological quality of clinical practice guidelines. The PubMed search engine (http://www.ncbi.nlm.nih.gov/pubmed) was used to perform a literature search of the MEDLINE database for relevant scientific publications. The key words used to search each question are shown. Only complete articles published in English or Spanish were selected. No specific period of inclusion was defined, although authors were instructed to inform mainly on the most recent evidence in the literature. The complete text has been discussed and approved by all authors. The criteria used to evaluate the strength of the recommendations and the quality of the evidence are summarized in Table 1. Possible conflicts of interest associated with all members of the panel of experts are listed at the end of the document.

Table 2. Strength of recommendation

Strength of recommendation	
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for 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.

CLASSIFICATION OF FEBRILE NEUTROPENIA RISK

1. – What tools exist to determine risk in a patient with FN? When should they be applied and in what contexts?

Search terms: "Risk factors" "Risk stratification", "Febrile neutropenia", "Cancer patients".

Recommendations:

1. Patients presenting with FN should undergo risk assessment for complications, preferably in the first hour of contact with the healthcare system (A-II).
2. The MASCC (Multinational Association for Supportive Care in Cancer) risk index is a prognostic scale that can be used to assess the risk of complications in patients with FN (B-II).
3. A patient with a MASCC risk index score of <21 is defined as high risk (B-II) and should be hospitalized and receive intravenous empirical antibiotic treatment (B-II).
4. A patient with a MASCC risk index score of ≥ 21 is defined as low risk (B-II). Some of these patients may be candidates for a regimen of oral antibiotics and can be managed as outpatients, provided that they are not receiving induction chemotherapy for acute myeloid leukemia and are not in the pre-engraftment phase of allogeneic hematopoietic stem cell transplantation (B-II).
5. Clinical criteria can also be used to determine risk in patients with FN.
6. Patients with an ANC ≤100/mm^3, expected neutropenia duration of >7 days, and/or significant comorbidities (hypotension, pneumonia, gastrointestinal symptoms, neurological symptoms) are considered high risk. These patients should be admitted to hospital and receive intravenous empirical therapy (A-II).
7. Patients with ANC <500/mm^3, expected neutropenia duration ≤ 7 days and having no or few comorbidities or significant evidence of renal or hepatic impairment are classed as

low-risk. These patients may be candidates for oral empirical therapy and outpatient care (A-II).

Summary of evidence

Various societies have developed action guidelines. These include the *Infectious Diseases Society of America* (IDSA),[42] the *European Society of Medical Oncology* (ESMO),[2] the *National Comprehensive Cancer Network* (NCCN),[43] and the *American Society for Clinical Oncology* (ASCO).[44] The *Multinational Association for Supportive Care in Cancer* (MASCC) risk index score is a validated instrument for measuring the risk of medical complications of FN.[45–48] The MASCC risk index score can be used as an alternative to clinical criteria.

The Clinical Index of Stable Febrile Neutropenia (CISNE) is a validated scoring system developed to predict serious complications in outpatients with solid tumors receiving mild- or moderate-intensity chemotherapy.[49] It is of limited application in hematology patients.

The *Infectious Diseases Society of America* (IDSA) has developed criteria to classify patients at high and low risk for FN complications:

High-risk

High-risk FN patients are defined as those with any of the following characteristics:

- ANC ≤100/mm^3 with an anticipated duration of neutropenia of ≥ 7 days, or
- Evidence of comorbidities such as hemodynamic instability, oral or gastrointestinal mucositis that makes swallowing difficult or causes severe diarrhea, gastrointestinal symptoms (abdominal pain, nausea and vomiting, or diarrhea), new-onset mental or neurological changes, intravascular catheter infection, new pulmonary filtrates or hypoxia; underlying chronic obstructive pulmonary disease, evidence of liver failure (liver transaminase levels ≥ 5 times the upper limit of normal) or kidney failure (renal creatinine clearance <30 ml/min).

These characteristics of FN are seen in patients in the pre-engraftment phase of HSCT, mainly allogeneic, who receive myeloablative conditioning, and in patients with acute myeloid leukemia in the remission induction phase of chemotherapy.

Low-risk

Low-risk patients with FN are those with predicted neutropenia of <500/mm^3 and ≤7 days, with no comorbid conditions or evidence of significant liver or kidney dysfunction.

Patients who present evidence of sepsis and septic shock (sepsis syndrome with organ dysfunction) should be considered at high risk, hospitalized and receive initial empirical antibacterial therapy administered intravenously. In patients with evidence of septic shock, the possibility of admittance to an intensive care unit should be considered.[50]

The *National Comprehensive Cancer Network* (NCCN) has developed similar criteria to those of the IDSA, with one exception. Under high-risk, they add hospitalization at the time when fever develops, uncontrolled neoplasia (partial remission in leukemia or progression of the disease after more than two cycles of chemotherapy in other hematologic malignancies), receipt of alemtuzumab in the previous two months and a MASCC risk index score < 21. Under low-risk, they consider that most patients are outpatients when a fever develops and that none of the previous criteria apply. The NCCN guidelines define an intermediate-risk category for complications if any of the following criteria apply: autologous HSCT, lymphoma, chronic lymphocytic leukemia, multiple myeloma, treatment with purine analogues or predicted duration of neutropenia of 7 to 10 days.

The MASCC risk index score claims to be more of a diagnostic tool for calculating risk at the patient's bedside (Table 3). The maximum possible score is 26. A score of ≥21 predicts which patients are considered to be at low risk of complications (<2%) and can be safely and effectively managed as outpatients with a course of empirical oral antibiotics. The MASCC risk index correctly classifies low- and high-risk in 98% and 86% of cases respectively, with sensitivity,

specificity, PPV and NPV values of 95%, 95%, 98% and 86%, respectively. The misclassification rates range from 10 to 29%.[44]

If patients initially classified as low-risk with “complicated infections” (visceral leishmaniasis, sepsis, non-necrotizing skin or soft-tissue infections of >5 cm in diameter, necrotizing soft-tissue infection (NSTI) of any size, or oral mucositis grade 2 or above (WHO)) are reclassified as high-risk patients, the predictive value of the model increases.[51] In addition, the MASCC risk index score can predict the risk of death: for a score of <15, the risk of death is 29%, for scores between15 and <21, the risk Is 9%, and for scores of ≥21, the risk of death is 2%. A retrospective cohort study suggested that C-reactive protein >15 mg/dL added to a high-risk MASCC index score is associated with a greater overall risk of mortality at 30 days, compared with C-reactive protein <15 mg/dL.[52]

The MASCC risk index score has been criticized: there is a clear subjective component in the definition of “symptom severity”, one of its key criteria is not precisely defined, and duration of neutropenia is not included as a criterion. For this reason, patients undergoing induction chemotherapy or preparative conditioning for HSCT should always be considered “high risk”. Another criticism is that the tool was developed using heterogeneous patient populations and has occasionally shown low sensitivity for detecting complications (36%).[53] This was probably due to the fact that all patients were outpatients and the rates of hypotension, dehydration and invasive fungal infections were low. Hence only three criteria were used to make their prognostic assessment.

In spite of everything, it should be remembered that clinical judgment, taking into consideration patient comorbidities, general clinical characteristics and functional capacity, together with psychosocial, organizational and logistic factors, continues to play a crucial role in risk stratification and decisions concerning discharge from hospital.

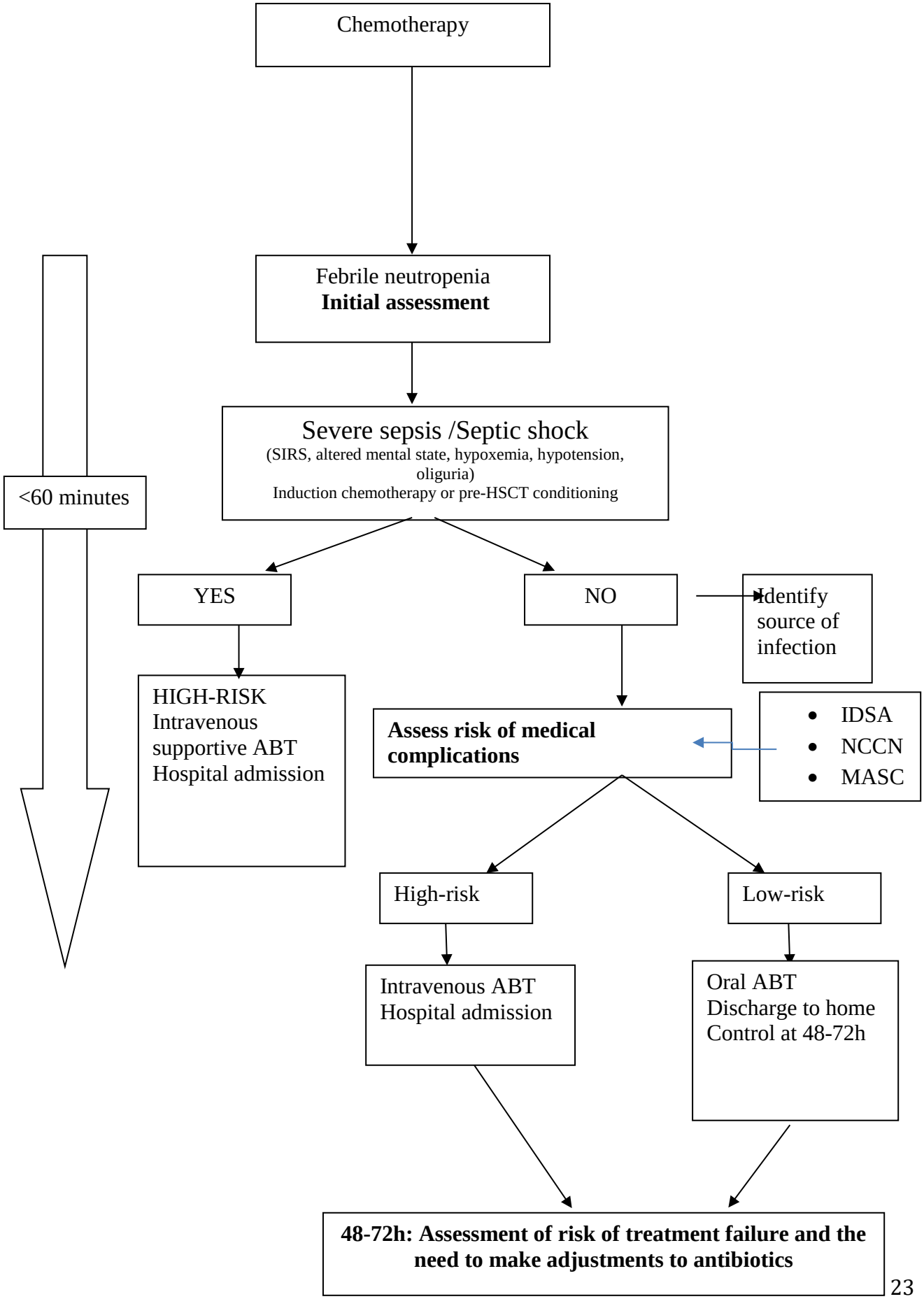
After 48-72 hours, clinical response should be evaluated and the need to adjust the antibiotic treatment in accordance with the microbiological results. The flow chart showing the process of evaluation of a patient with FN is represented in Figure 2.

Table 3. MASCC risk index score

Characteristics	Score
Burden of illness: no symptoms or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor/ lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Burden of illness: General clinical status in relation to FN
Patients with scores ≥ 21 have a low risk of complications. The scores attributed to the “burden of illness” variable are not cumulative. The maximum theoretical score is 26.

Figure 2. Flow chart showing the process of evaluation of a patient with FN



DIAGNOSTIC MANAGEMENT

1. – What microbiology diagnostic methods should be performed for patients with FN?

Search terms: "Febrile neutropenia" AND "Etiology". "Febrile neutropenia" AND "Microbiological diagnosis".

Recommendations

1. It is recommended that at least two, and preferably three, sets of blood cultures be collected from any patient with FN, whether they are in-patients or seen in the emergency room, high-risk or low-risk. Blood should be drawn through all available catheterized venous access in the patient, paying special attention to long-term devices, as well as samples taken by venipuncture from peripheral vein sites (A-I).
2. If an infection of extravascular origin is suspected, it is recommended to send representative samples from the possible focus of infection. Rapid microbiological tests can be performed on these samples (A-I).
3. For patients being monitored in an outpatient setting with symptoms or radiological signs of respiratory infection, rapid urine antigen tests for the detection of *Streptococcus pneumoniae* and *Legionella pneumophila* antigens can be used (A-II).
4. During annual flu epidemics, molecular methods should be used for early diagnosis. In the case of flu, rapid techniques on nasopharyngeal swabs are preferred (B-II).
5. If the patient presents diarrhea, it is advisable to request a *Clostridium difficile* toxin stool test, on which rapid immunochromatographic assays or PCR can be performed (C-III).

Summary of the evidence

Since the signs and symptoms of infection can be attenuated in patients with neutropenia, fever can be the only indicator of an infectious process and it is necessary to draw blood cultures to diagnose infection. Blood for cultures should be drawn in pairs, each extraction

being split between two culture bottles, one for aerobic microorganisms, the other for anaerobes. At least two, or preferably three, sets of blood should be drawn for culture, using all available access lines in the patient, especially long-term central lines.[42] The purpose of drawing several sets of blood for culture is twofold: first to increase the sampling yield, and second, in the case of growth of microorganisms with low pathogenic potential, such as those that are part of the normal saprophytic flora of the skin, to differentiate between blood culture contamination resulting from inadequate skin antiseptic before drawing the blood and true bacteremia. The recommended volume for each blood culture bottle is 10 ml in adults, thus increasing the yield over lower volumes by 3–5% per ml.[54–57] (Figure 3).

Drawing blood for culture through vascular catheters can help distinguish whether the source of the bacteremia is the catheter without having to remove it first. According to this technique, if the differential time to positivity of growth detected in a blood culture drawn through a catheter is ≥2 hours before one drawn simultaneously by venipuncture, the source of the bacteremia is probably catheter-related.[58] A limitation of this method is that it requires the inoculated volume in each blood culture bottle to be the same. If there is suspicion of catheter-related bacteremia due to inflammation or discharge at the insertion site, before removing the catheter, samples can be obtained from the 2 cm of skin surrounding the catheter insertion site for semiquantitative Gram stain and culture. Cultures yielding counts of ≥15 CFUs can be considered positive. Nevertheless, their greatest use is their negative predictive value for catheter-related infection.[59]

The major drawback with blood cultures is that they are slow, requiring several hours of incubation before they become positive. This depends on the bacterial inoculum, which, together with the problems linked to slower growing intracellular bacteria, would explain why the rate for positive blood cultures ranges between 30% and 40%. In order to speed up the time to discovering the cause of the infection and optimizing antimicrobial treatment, most centers have

implemented mass spectrometry methods (MALDI-TOF) or techniques based on amplification of bacterial DNA (PCR) that can identify the microorganism in less than 60 minutes when compared with the positive blood culture,[60–62] regardless of how the blood culture is conventionally processed in the laboratory. In recent years, molecular techniques have been developed for direct application on the sample[63–65] in an attempt to further reduce the response time. Nevertheless, sensitivity and specificity can vary depending on patient selection. Consequently, the blood culture remains the gold standard among microbiological techniques for the diagnosis of bacteremia and sepsis because the microorganism can be isolated for antimicrobial susceptibility testing.

Likewise, it is recommended to take samples from possible foci of infection so that rapid techniques, especially stains and PCR, can be performed to guide diagnosis.Depending on the quality of the sample and the experience of the microbiologist, the positive predictive value can be very high. If urinary tract infection is suspected, apart from the conventional urine culture and Gram stain, early detection techniques based on flow cytometry are being implemented with response times of around 10 minutes and very high positive predictive values, as well as turbidimetric methods applied to precultures.[66–70]

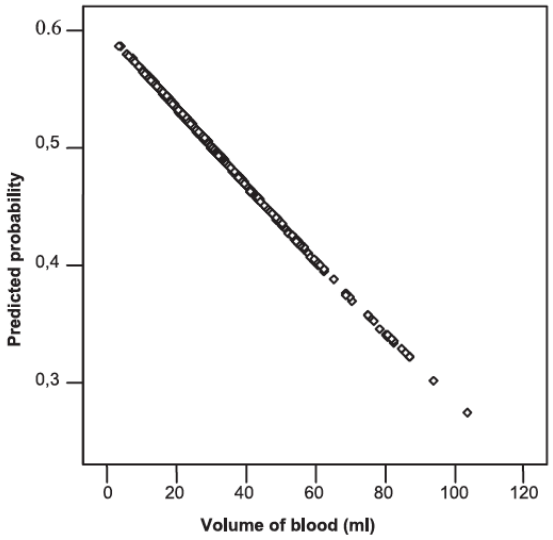
For low-risk neutropenic patients being managed as outpatients who present in the emergency room with fever and symptoms or radiological signs of respiratory infection, rapid urine tests with very high PPVs and NPVs should be performed for detection of *S. pneumoniae* and *L. pneumophila* urinary antigens. These are rapid procedures with a turnaround time of less than 20 minutes and very high sensitivity and specificity,[71–73] although some false positives have been described in nasopharyngeal carriers of *S. pneumoniae* and those who have received pneumococcal vaccination.[74] The sample can be collected once empirical antibiotic therapy has started, since detection of excreted antigens is not affected by the activity of the antimicrobials. In any case, it is recommended to take representative samples from the respiratory tract for culture.

During the annual flu epidemics, early microbiological screening and testing for influenza virus should be carried out. There are rapid molecular techniques based on isothermic amplification of viral RNA from the nasopharyngeal exudate that do not need prior treatment of the sample, have a response time of less than 30 minutes and a high PPV.[75] In this case, to increase the sensitivity of the technique, it is recommended to take the sample before initiating antiviral treatment. These techniques have a very high PPV but false negatives may appear if the test is carried out more than 48 hours after the onset of symptoms when the viral load is starting to decrease.[76]

Because of the continuous antimicrobial treatment and prophylaxis, especially with fluoroquinolones and clindamycin, many hematologic patients become colonized with strains of *C. difficile,* and between 20 and 30% develop *C. difficile* infection and it is not useful to apply scales that predict risk of recurrence or poor prognosis in these patients.[77] Consequently, a useful diagnostic approach to be taken with a patient with FN and diarrhea may be to ask for a *C. Difficile* toxin test. There are rapid immunochromatographic tests with a very high NPV and a turnaround time of less than 20 minutes,[78] as well as real-time PCR methods that can be performed directly on a sample with response times of less than 2 hours[79] and very high PPVs and NPVs.

Figure 3. Relationship between the volume of blood and probability of a positive culture (OR, 0.987; 95% CI, 0.976-0.998; p=0.018). An inversely proportional relationship can be

observed in both the figure and the table between the volume of blood inoculated and the percentage of positive cultures. Modified from Bouza E, et al.[55]



Blood vol (ml)	No. of positive episodes/total (%)
<20	63/107 (58.9)
20–30	123/234 (52.6)
30–40	65/143 (45.5)
>40	47/117 (40.2)

[a] $P = 0.022$.

2. – When and how should pre-emptive screening for fungal infection be carried out?

Search terms: "Febrile neutropenia AND fungal infection diagnosis", "Febrile neutropenia AND investigation for invasive fungal infection".

Recommendations

1. In patients with FN, pre-emptive screening for fungal infection should be considered when fever persists for 4-7 days after having started broad-spectrum antibiotics, expected duration of neutropenia is > 7 days, and in clinically compatible cases (A-I).
2. Blood cultures are the microbiological test of choice for the diagnosis of yeast infections (A-I).
3. In clinically stable patients who are not receiving antifungal prophylaxis against filamentous fungi, it is recommended to screen for *Aspergillus* infection by carrying out serial testing for circulating galactomannan (GM) in serum twice a week. In the event of a positive GM test, a CT scan of the lungs is recommended (A-I).
4. In patients receiving antifungal prophylaxis against filamentous fungi, a CT scan of the thorax is recommended if fever persists (>7 days after initiating broad-spectrum antibiotics, with no other identifiable cause of fever). In the event of findings suggestive of invasive fungal infection, bronchoscopy is recommended for galactomannan testing, and pan-fungal PCR on the bronchoalveolar lavage (BAL) fluid. If results are negative, lesion puncture is recommended (B-II).

Summary of evidence

Preemptive screening for fungal infection should be individualized according to the suspected fungal infection, the host characteristics and whether antifungal prophylaxis is being given or not. Hematogenous spread is the most common clinical manifestation of yeast infections, especially in *Candida* species, whereas filamentous fungi, such as the *Aspergillus* species or the Zygomycetes, mainly manifest in the neutropenic patient in the form of angioinvasion with

pneumonia or infarction in the pulmonary parenchyma. Some fungi capable of forming spores very similar to yeasts, such as the *Fusarium* species, may present in mixed clinical forms with lung involvement and hematogenous spread.

The clinical manifestations of fungal infection in neutropenic patients are not always obvious, so that pre-emptive screening for fungal infection does not only depend on the clinical signs. A diagnosis of fungal infection should be considered in hematologic patients with high-risk neutropenia who present compatible clinical symptoms (new-onset respiratory signs and symptoms, metastatic skin lesions, neurological alterations or otherwise unexplained abdominal pain) and also in those with persistent fever (4-7 days after initiating broad-spectrum antibiotics) and predicted duration of neutropenia of > 7 days.

In patients with FN, blood cultures will help diagnose *Candida* spp. infections. A diagnosis of infection caused by filamentous fungi will be based on a combination of the clinical characteristics of the patient and data obtained from radiological, anatomopathologic and microbiological tests and studies.[80] Antifungal prophylaxis against filamentous fungi reduces the sensitivity of microbiological tests,[81] so that testing for this type of infection should differ according to whether the patient is receiving prophylaxis or not.

In patients with high-risk neutropenia not receiving antifungal prophylaxis for filamentous fungi, it is recommended to screen for fungal infection so that a pre-emptive antifungal treatment strategy can be initiated. Serum fungal biomarkers such as galactomannan twice a week on blood are recommended for this purpose.[82] Two positive values (>0.5) have high sensitivity and a high NPV for a diagnosis of aspergillosis.[83] The ECIL guidelines recommend that a single positive GM index of 0.7 or above should prompt a diagnostic work-up.[84] The result of this test should be available within 24h. A combination strategy of galactomannan and PCR could be used for an earlier diagnosis of aspergillosis.[85] If these microbiological methods give positive results, a chest CT scan should be carried out even if there are no clinical respiratory signs and symptoms. If the

serum galactomannan values are negative, but the patient does show clinical respiratory signs, it is advisable to carry out a lung CT scan, followed by bronchoscopy with bronchoalveolar lavage if the findings are compatible with fungal infection. The bronchoalveolar lavage (BAL) fluid samples can be used in GM testing and panfungal PCR. A sinus CT scan should also be considered.

In patients with FN who are receiving antifungal prophylaxis against filamentous fungi, there is very little information about how to make an early diagnosis of fungal infection. The decrease in fungal load after prophylaxis means that the commonly used diagnostic techniques commonly have a limited role to play. Recent studies[86,87] have shown that the strategy of serial serum galactomannan and PCR assays is associated with a high false positive rate due to the low pre-test probability of breakthrough fungal infection. Nevertheless, GM and PCR values on BAL fluid seem to be less affected by the use of antifungal prophylaxis.[88] In this case, the recommended cut-off galactomannan index in BAL fluid is 1.

Although there is scant scientific evidence of how to make an early diagnosis of fungal infection in patients receiving antifungal prophylaxis against infections caused by filamentous fungi, a chest CT scan is recommended if fever persists >7 days after starting broad-spectrum antibiotics with no other obvious cause of fever, or if there are compatible clinical symptoms. If the findings suggest breakthrough invasive fungal infection, bronchoscopy is recommended for a GM assay and panfungal PCR on the BAL fluid. If these microbiological results are both negative, lesion puncture is recommended.

3. – Are biomarkers useful for infection diagnosis in FN and for determining length of antibiotic treatment?

Search terms: “Biomarkers and infection diagnosis”, “Febrile neutropenia”, “Bacteremia and biomarkers”, “Length of antibiotics in febrile neutropenia”.

Recommendations

1. Biomarkers are not recommended as a guide to antibiotic use in FN, due to the lack of studies demonstrating the safety and usefulness of basing clinical decisions on their results (B-III).
2. It has been demonstrated that neutropenic patients with bacteremia present significantly higher procalcitonin (PCT), C-reactive protein, IL-6, and presepsin levels than those without bacteremia. (A-II). The possible impact of this information on the future management of FN is yet to be clarified.
3. Biomarkers are not useful for determining length of antibiotic treatment (A-II).
4. C-reactive protein levels, especially those that are elevated (>20-30 mg/dl), are correlated with greater mortality. This relationship has not been demonstrated with the other biomarkers (PCT, presepsin, IL-6) (C-III).

Summary of the evidence

Fever in the neutropenic patient (post-chemotherapy, post-transplantation) can be due to different causes: both infectious (bacterial, viral or fungal) and inflammatory (engraftment syndrome, GVHD, cytokine release syndrome, systemic inflammatory response syndrome (SIRS), tumor progression, and so on). The clinical manifestations can occasionally be impossible to differentiate from each other.

Infection in the neutropenic patient can progress rapidly and lead to death, if it is not treated early and correctly. On the other hand, it should be borne in mind that antibiotic treatment for a febrile syndrome that has a non-infectious cause can contribute to toxicity and the development of bacterial resistance, without being effective in controlling the fever. Apart from taking a comprehensive anamnesis and carrying out a thorough physical examination, it would be very helpful to have a few quick and reliable objective criteria to help us determine whether the

fever in these patients is infectious in origin or not. Some attempts have been made to use certain biomarkers of infection for this purpose.

The biomarkers that have been investigated most are:

a) Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin secreted by the C-cells of the thyroid gland in response to hypercalcemia. It is thought to be secreted by the liver and peripheral blood mononuclear cells in situations of infection or inflammation, modulated by lipopolysaccharides and sepsis-related cytokines (the infectious stimulus). The secretion of PCT begins 4 hours after the infectious stimulus and peaks at 8h. It is negativized when the stimulus is under control. The result is rapid (2h) and the cost moderate.[89]

b) C-reactive protein is an acute-phase reactant, synthesized in the liver, mainly in response to the production of IL-6, which is produced in response to infectious stimuli and inflammation. It binds to polysaccharides in pathogens, activating the complement pathway. Secretion of C-reactive protein occurs 4-6h after the stimulus and peaks at 36h. Analysis is automated, rapid and low-cost.[89]

c) Presepsin is a soluble (N-terminal fragment) molecule derived from the CD14 protein, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. It is secreted in the first 2h of the infectious stimulus and is a marker of the early stage of infection. Given that its precursor CD14 is expressed on the surface of neutrophils and monocytes and internalized during bacterial phagocytosis, this biomarker is strongly associated with bacterial infections. In neutropenic situations, presepsin may not be a reliable diagnostic marker, given that CD14 is expressed on neutrophils or monocytes,[90,91] although some authors have demonstrated that biomarker levels do not change in neutropenia.[92]

Biomarkers of infection have demonstrated their usefulness in ruling out bacterial infection in certain populations, such as pediatric populations, but there is very little information available about their use in immunosuppressed patients.[90,91,93,94] Different studies have demonstrated that neutropenic patients with bacteremia have higher PCT, C-reactive protein, and IL-6 levels than those without bacteremia.[93] One prospective observational study of 52 patients with neutropenia after hematopoietic stem cell transplantation reported that presepsin was a better marker than PCT for sepsis caused by gram-negative bacilli.[95] This biomarker could be advantageous for early diagnosis of bacterial infection in cases of recurrent fever in patients already receiving antibiotic therapy or who have recently experienced treatment failure.[92] For gram-positive microorganisms or localized infections without associated bacteremia (pneumonia, abscesses, central nervous system (CNS) infections, and so on), C-reactive protein may be more sensitive.[89,95,96]

Nevertheless, because the available studies on different biomarkers are few, most of them do not have NPV data, and all of them show modest sensitivity values for the detection of bacteremia, these biomarkers cannot at present be recommended for deciding whether to initiate antibiotics in patients with febrile neutropenia, nor have they demonstrated their usefulness in defining the length of antibiotic therapy.[90,93,94.]

EMPIRICAL ANTIBIOTIC TREATMENT

1.- What empirical treatment strategies are there for patients with NF?

Search terms: “Febrile neutropenia”, “Empirical antibiotic treatment”.

Recommendations

1. Any febrile patient with an ANC of <500/mm^3 and those with ANC of 500-1,000/mm^3 and predicted to decline imminently should receive early empirical antibiotic treatment (A-II) with an appropriate broad-spectrum antibiotic (A-I) and a bactericidal agent.

2. Surveillance programs (antimicrobial stewardship) established in the center for the appropriate use of antibiotic treatment should be taken into consideration (B-III).
3. A strategy of *dose-escalation* can be applied in patients with an uncomplicated clinical presentation, no previous colonization/infection with multidrug-resistant bacteria, and in centers where there is a low incidence of drug-resistant microorganisms (B-II). In other situations, a *de-escalation* strategy should be applied (B-II).

Summary of the evidence

Numerous guidelines have been published on sequential empirical therapy.[42,97–99] Nonetheless, it is necessary to critically review these guidelines on a regular basis as a result of changes in the pattern of causative microorganisms, the appearance of multidrug-resistant (MDR) organisms, the shortage of new antibiotics, especially those against gram-negative bacilli, and the increasing use of immunomodulatory drugs.

For the choice of empirical antibiotic treatment, a series of factors should be taken into consideration (Table 4). These include: the risk of infection associated with the category of neutropenia (low-risk versus high-risk – see the corresponding section), potential foci of infection based on the clinical data (mucositis, catheters, etc.), clinical repercussions (hypotension, sepsis, septic shock, etc.), the expected epidemiology based on epidemiological data for each center and individual unit (resistance patterns and specific situations of endemic MDR bacteria), as well as the existence of previous infections or colonization by microorganisms of epidemiological significance (ESBL- AmpC- carbapenemase-producing Enterobacteriaceae, etc.), recent use of antibiotics, either as prophylaxis or treatment, and the presence of antibiotic allergies. Bactericidal antibiotics should be chosen, using appropriate dosage regimens based on their PK/PD properties and proven evidence of efficacy.

Without abandoning the general principles of treatment in these patients, there is a

tendency to individualize treatments participating in stewardship programs for appropriate control of antibiotic use established in the center,[100,101] and to avoid using excessively strict, often unnecessary protocols of empirical therapy with high economic and ecological costs.

The aim of such strategies is to limit antibiotic use that favors the development or selection of MDR, specifically carbapenems and combination regimens, and also to avoid toxicity. Depending on the risk of infections caused by multidrug-resistant bacteria, these strategies can be applied in the initial phase ("escalation" strategy: amplification), or after subsequent reassessment, with sequencing and limiting the length of therapy in accordance with the clinical evolution and the microbiological data available ("*de-escalation*" strategy: simplification). A *dose-escalation* strategy can be used when the clinical presentation is uncomplicated, local epidemiology has a low prevalence of MDROs, and the patient has not been previously infected / colonized with MDROs. In doubtful situations, a *de-escalation* strategy that ensures early initiation of effective treatment is recommended.[102]

Finally, given the possibility of concomitant polymicrobial infections, the risk of secondary bacterial infection during the course of the infection, and the risk of fungal infection in prolonged neutropenia, the effectiveness and adequacy of the initial treatment regimen should be re-evaluated to assess the need for a change of initial regimen or the sequential addition of other antibiotics, including antifungal treatment (which will be dealt with elsewhere in this document).

Table 4. Factors to consider for the choice of empirical antibiotic therapy

- ✓ Risk of infection associated with the category of neutropenia
  - Low-risk *vs* high-risk
- ✓ Potential foci of infection based on clinical data (mucositis, catheters, etc.)
- ✓ Clinical repercussion (hypotension, sepsis, septic shock, etc.)

- ✓ Expected epidemiology (ESBL- /AmpC- /carbapenemase-producing Enterobacteriaceae, etc.)
  - Epidemiology of the center / unit
  - Previous infections
  - Colonization
- ✓ Recent use of antibiotics (prophylaxis, treatment)
- ✓ Allergies to antibiotics

2. – What is the empirical antibiotic treatment of choice when there is no obvious clinical focus of infection?

Search terms: “Febrile neutropenia”, “Empirical antibiotic treatment”, "Fever unknown origin”.

Recommendations

1. It is recommended to use a beta-lactam antibiotic with antipseudomonal activity as monotherapy, or in combination with another antibiotic, depending on the risk of infection due to multidrug-resistant microorganisms and clinical presentation (A-I).

2. For the escalation strategy:
   - 2.1 Use of piperacillin-tazobactam (A-I), or cefepime (A-I), or ceftazidime (B-II) is recommended.
   - 2.2 In settings with a high prevalence of ESBs, cephalosporins and piperacillin-tazobactam in monotherapy are not recommended (B-II).
3. For the de-escalation strategy:
   - 3.1 Imipenem or meropenem in monotherapy are recommended for use (B-II), or a combination of antipseudomonal beta-lactam plus an aminoglycoside or a fluoroquinolone (if it has not been used as prophylaxis) (B-III). Carbapenems should be reserved for critically ill patients.

3.2 The aminoglycoside should be given in a single daily dose (A-II). The need to continue the aminoglycoside should be reassessed at 48-72 hours.

3.3 If there is risk of infection due to multidrug-resistant nonfermenting gram-negative bacilli, it is recommended to combine the beta-lactam with the lowest antimicrobial resistance rate in the center + amikacin or colistin (B-III).

3.4 The need for empirical treatments with other combinations can be considered, according to local epidemiology or in outbreak settings (C-III).

3.5 The use of antibiotics with activity against gram-positive cocci resistant to beta-lactams (vancomycin, daptomycin, linezolid) would be indicated only in cases of hemodynamic instability and/or risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection (B-III).

3.6 The empirical addition of vancomycin to initial antibiotic therapy is not recommended if fever persists at 3 days (A-I) .

3.7 In hemodynamically unstable patients, treatment should be started immediately with a broad-spectrum beta-lactam with antipseudomonal activity together with an antibiotic active against beta-lactam-resistant gram-negative bacilli, and a drug with activity against methicillin-resistant gram-positive cocci (B-III). In patients with septic shock not receiving antifungal prophylaxis, consider adding active treatment against *Candida* spp to the initial regimen (C-III).

Summary of the evidence:

In this section we refer to empirical treatment for patients with high-risk FN.

Monotherapy

Beta-lactam monotherapy as the initial empirical antibacterial choice has been shown to be as effective as combination treatment with an aminoglycoside, even in cases of bacteremia

and profound neutropenia, with the exception of complicated cases or settings where multidrug-resistant bacteria are endemic. The recommended antibiotics are high-dose beta-lactams with antipseudomonal activity.[103–113]

As a result of epidemiological changes in the prevalence of infections caused by gram-positive cocci, ceftazidime has been in restricted use in recent years because of its low activity against these pathogens, as well as the increased incidence of infections caused by ESBL-producing Enterobacteriaceae (both plasmid-mediated and AmpC-type chromosomal beta-lactamases), which would not be properly treated.

In a meta-analysis published in 2006, increased mortality from any cause was observed among patients with FN treated with cefepime in monotherapy.[114,115] A later meta-analysis with new data found no differences in mortality.[116] Although the authors of the first analysis questioned this finding,[117,118] the FDA considers cefepime monotherapy to be adequate.

For years, it has been recommended to avoid piperacillin-tazobactam in patients at high risk of fungal infections owing to its association with false positive GM results in blood (through contamination in the drug production process).[119,120] It has now been shown that this contamination is absent with new formulations of the drug.

Finally, carbapenems (imipenem and meropenem) have become established in many centers in recent years as the antibiotics of choice for empirical monotherapy of FN as a result of the increased incidence of ESBL-producing Enterobacteriaceae. This has led to overuse, with the potential risk of favoring selection of resistant bacteria via diverse resistance mechanisms, which currently constitutes a world health issue. It is recommended to limit their use, both in initial empirical treatment, by avoiding them in patients who do not have a severe clinical presentation and are not at risk of infection with resistant microorganisms (*escalation* strategy), and at later reevaluations of empirical therapy, via sequencing (*de-escalation*) if they are not necessary, as well as shortening the length of antibiotic therapy.

Combination therapy

Empirical combination treatment consisting of a beta-lactam and an aminoglycoside (or a fluoroquinolone, if it has not been used as prophylaxis) would be indicated in centers with a high prevalence of multidrug-resistant gram-negative bacilli and in patients with complicated clinical presentations. It should also be considered in patients who have received beta-lactams previously. The potential advantages of combination treatment with aminoglycosides include the increased antibacterial spectrum, if there is a possibility of multidrug-resistant bacteria, the potential synergistic effect against certain microorganisms (*P. aeruginosa*) and their rapid, concentration-dependent bactericidal action.

The need to continue the aminoglycoside should be re-evaluated on day 3 or 4. It can be stopped in the majority of cases, so reducing the associated risk of nephrotoxicity and ototoxicity. Use of a single daily dose is associated with a lower risk of nephrotoxicity.

The appearance of MDR (multidrug-resistant *P. aeruginosa* susceptible only to colistin, carbapenemase-producing Enterobacteriaceae, etc.) is the reason why it is essential to take the local epidemiology of individual institutions into account for initial empirical treatment of onco-hematology patients. In this scenario, an “amplified” empirical combination can be proposed, preferably agreed in consensus with the team of specialists at each center. The following possibilities could be used: colistin, aztreonam, extended infusion of carbapenems, triple therapy with tigecycline, depending on local epidemiology. In such situations, reassessment of the initial regimen at 48-72 hours is even more important, making dose adjustments or adding other antibiotics according to clinical evolution and the microbiological results.

Although there is at present no established indication for beta-lactams with beta-lactamase inhibitors (BLBLIs) (ceftazidime/avibactam and ceftolozane/tazobactam) and there are no data in this population, they could be taken into consideration, as they may be useful in

settings with a high prevalence of MDR gram-negative microorganisms.

Use of agents with specific activity against Gram-positive organisms.

Use of initial empirical antibiotics with specific activity against methicillin-resistant Gram-positive cocci in patients with FN has not been shown either to lead to a more favorable evolution or lower mortality rates.[121,122] Adding them to empirical treatment would be indicated in any patient with hemodynamic instability or previous evidence of MRSA colonization, and the need to continue them should be reevaluated at 48-72 hours. The presence of mucositis does not justify their use if empirical treatment includes an antibiotic with activity against Gram-positive cocci. Nor are they justified in patients with risk factors for viridans group streptococci (VGS) bacteremia (mucositis, fluoroquinolone prophylaxis, high-dose cytarabine), given the low rates of resistance to VGS observed in our environment.

The addition of empirical vancomycin is not recommended if fever persists at day 3 despite broad-spectrum antibacterial treatment.[123] If an infection caused by Gram-positives is suspected, the main therapeutic options are vancomycin, daptomycin, and linezolid. Except where there is specific evidence of vancomycin resistance, there are no conclusive data at present to support recommending daptomycin or linezolid over vancomycin for FN.

There are data on the use of daptomycin in infections caused by Gram-positive microorganisms in onco-hematology patients, which indicate that it is a safe and effective therapeutic alternative.[124–126] It should never be used if respiratory infection is suspected, since it is inactivated by lung surfactants. One advantage of daptomycin over vancomycin is the absence of nephrotoxicity, so that in situations where this limitation might apply, the use of daptomycin is recommended before vancomycin. If *S. aureus* bacteremia is suspected, it is always recommended to administer high-dose daptomycin as a single dose.

With respect to linezolid, its use in onco-hematology patients is frequently limited because of thrombocytopenia, a common adverse effect associated with prolonged use of this

drug (more than 2 weeks), which would overlap with the significant myelosuppression associated with both treatment and illness in these patients. Delays in bone-marrow recovery have not been observed in hematologic patients receiving a short course of linezolid treatment.[127] Linezolid use is also controversial in cases of suspected but not confirmed bacteremia, following the results of a study that observed that the risk of mortality was higher in infections (catheter-related bacteremia) treated with linezolid.[128]

Ceftaroline is another antibiotic with activity against Gram-positive pathogens, including MRSA, although there are at currently no data on its use in this population.

Patients with hemodynamic instability

In patients who are hemodynamically unstable or have criteria for septic shock, combination treatment is prescribed, including a beta-lactam with antipseudomonal activity and an antibiotic with activity against beta-lactam-resistant gram-negative bacteria (aminoglycoside, colistin, according to local epidemiology) and a drug with activity against methicillin-resistant Gram-positive cocci (daptomycin or vancomycin). In patients with septic shock not receiving antifungal prophylaxis, consider adding active treatment against *Candida* spp to the initial regimen.

3.- What is the empirical treatment of choice when there is a clear clinical focus of infection?

Search terms: “Febrile neutropenia”, “Empirical antibiotic treatment”

Recommendations

1. Oropharyngeal mucositis /esophagitis

1.1. In patients with mild forms of mucositis, anaerobic coverage is not essential and cefepime may be used (B-III).

1.2. In more severe forms, ensure anaerobe coverage with piperacillin-tazobactam, imipenem or meropenem (A-III).

1.3. Consider initiating antiviral and/or antifungal treatment in patients not receiving prophylaxis who have suggestive oral lesions or symptoms compatible with esophagitis (C-III).

2. Neutropenic enterocolitis (typhlitis)

2.1. Start treatment with a broad-spectrum antibiotic such as piperacillin-tazobactam, imipenem or meropenem that includes activity against gram-negatives, Gram-positives and anaerobes (A-III).

2.2. Consider adding treatment for *C. difficile* if there is a high index of suspicion (C-III).

3. Perianal infection

3.1. Performing a digital rectal examination is contraindicated in the neutropenic patient. Nevertheless a thorough examination of the perianal region is fundamental (B-III).

3.2. The treatments of choice are piperacillin-tazobactam, imipenem or meropenem (A-III).

3.3. If there is clinical suspicion of a perianal abscess, ensure active treatment against gram-negative bacilli, *Enterococcus* spp. and anaerobes (A-III).

4. Skin and soft tissue infection (SSTI)

4.1. Start treatment with a broad-spectrum, antipseudomonal beta-lactam agent with activity against Gram-positive cocci, including *S. aureus* (A-III).

4.2. Consider adding an antibiotic with activity against MRSA if there is a history of previous colonization/infection (B-III).

4.3. It is recommended to obtain a sample of tissue for microbiological and histopathologic analysis from any skin lesion suspected of being a source of infection (B-III).

4.4. The possibility of a serious necrotizing soft tissue infection (NSTI) should always be ruled out (B-III).

4.5. If a serious necrotizing infection is suspected, it is recommended to use agents such as clindamycin that inhibit protein synthesis, and so inhibit toxin production (A-III).

5. Intravascular catheter-related infection

5.1. Start treatment with an antipseudomonal beta-lactam together with an agent with specific activity against drug-resistant Gram-positive organisms such as vancomycin or daptomycin (A-III).

5.2. Linezolid is not recommended in this situation (B-III).

5.3. If the infection is considered serious and the catheter is the obvious source of infection, remove the catheter promptly before the microbiological results are known (B-III).

6. Paranasal sinuses

6.1. Start treatment with a broad-spectrum antipseudomonal beta-lactam with activity against Gram-positive cocci, including *S. pneumoniae* and *S. aureus* (A-III).

6.2. In risk patients (prolonged neutropenia, corticotherapy), consider adding treatment with activity against *Aspergillus* or Mucorales, which can give a picture of sinusitis that is initially difficult to differentiate from one with a bacterial etiology (B-III).

7. Pneumonia

7.1. Start with a broad-spectrum beta-lactam with activity against *S. pneumoniae* and *P. aeruginosa* (A-III).

7.2. In critically ill patients, nosocomial cases and patients previously colonized/infected with MDR gram-negative bacilli, it is advisable to combine with a second antibiotic, according to local epidemiology (B-III).

7.3. If the infection is community-acquired and an atypical pneumonia is suspected, consider combining with fluoroquinolones or macrolides (B-III).

7.4. In patients with MRSA colonization or epidemiological settings of high endemicity, combination with an active agent such as linezolid or vancomycin must be considered. (B-III).

7.5. During flu epidemics, add empirical treatment with oseltamivir (C-III). Once samples have been collected and the results are known, continuation or withdrawal of treatment can be assessed.

7.6. In risk patients with bilateral infiltrates, consider other possible etiologies (*Pneumocystis jirovecii*, cytomegalovirus) (B-III).

8. Urinary tract infection

8.1. Start with a beta-lactam with antipseudomonal activity (A-III).

8.2. Consider adding a second antibiotic in critically ill patients, those with indwelling urinary catheters, and/or a previous history of colonization/infection with multidrug-resistant bacteria, according to local epidemiology (aminoglycoside, glycopeptide) (B-III).

9. Central nervous system infections

9.1. In cases of acute meningitis, antibiotic treatment should include a beta-lactam with activity against *S. pneumoniae* and *P. aeruginosa* with good penetration into cerebrospinal fluid (CSF) (cefepime or meropenem) and ampicillin to cover *Listeria monocytogenes* (A-III).

9.2. In risk patients with suggestive clinical forms, or patients with space-occupying lesions, consider other etiologies (*Cryptococcus*, *Listeria, Nocardia,* filamentous fungi, toxoplasmosis and *Mycobacterium tuberculosis* (B-III).

Table 5 summarizes the recommended empirical antibiotic treatments according to clinical focus of infection

Summary of evidence

Mucositis

Mucosal disruption favors infection with microorganisms that colonize the oral cavity and oropharynx. In this context, we should also take into account the bacteria that are part of the normal bacterial flora (*Streptococcus* spp, Gram-positive and gram-negative anaerobes, etc.), but it is also very important to consider colonization by microorganisms acquired within the hospital, which can take place within a few hours of hospital admission (gram-negative bacilli such as *P. aeruginosa*; and Gram-positive cocci, such as *Staphylococcus* spp.). For patients with severe mucositis, we will have to choose a broad-spectrum antibiotic treatment covering gram-negative, Gram-positive and anaerobic organisms. Except in the case of known colonization with Gram-positive cocci resistant to penicillin (*Streptococcus* spp.) or to methicillin (*S. Aureus*), empirical use of agents with specific activity against these microorganisms is not indicated.

Oral mucositis due to *Candida* spp. or to reactivation of a latent herpes simplex virus (HSV) may be indistinguishable from toxic mucositis, so that administration of antifungal and/or antiviral treatment should be considered for any patient not already receiving prophylaxis.[129] Samples should be collected for fungal culture and to determine HSV infection by PCR assay. If the results are negative, treatment should be withdrawn. If there is clinical suspicion of esophagitis (the symptoms may be only nausea and vomiting without dysphagia), also evaluate empirical antiviral and/or antifungal treatment (which is an acceptable empirical option compared to performing endoscopic procedures).

Neutropenic enterocolitis (typhlitis)

Neutropenic enterocolitis is a potentially very serious complication in the context of profound neutropenia secondary to cytotoxic chemotherapy.[130] In the strict sense of the term, typhlitis refers to inflammation of the cecum, although any segment of the intestine may be affected.

Broad-spectrum antibiotics with activity against aerobes and anaerobes should be started. If there is clinical suspicion, antifungal treatment against *Candida* spp. is indicated in patients without prophylaxis, as well as empirical treatment for *C. difficile*.[131]

Perianal infection

Digital rectal examination is contraindicated in patients with neutropenia because of the risk of triggering bacteremia. Nevertheless, a thorough exploration of the perianal region is fundamental.

If there is clinical suspicion of a perianal abscess, antibiotics with activity against gram-negative bacilli, *Enterococcus* spp. and anaerobes should be used. The possibility of severe forms of necrotizing fasciitis (Fournier's gangrene) should be ruled out.

Skin and soft tissue infections

During the evaluation of FN, an extremely thorough exploration should be carried out in search of skin lesions since they may be both the primary focus of infection as well as a manifestation of systemic disease (secondary septic focus). Nevertheless, assessment is difficult, giving rise to a broad differential diagnosis of both infectious and non-infectious processes (Sweet's syndrome, GVHD, toxicoderma etc.). For this reason, it is recommended to take a skin biopsy of any significant lesion for microbiological study and anatomopathologic analysis.

Skin barrier disruption (catheters, wounds, skin lesions with a different etiology) favors infection with skin-colonizing microorganisms (*Staphylococcu*s spp., microorganisms of nosocomial origin, etc.), which will have to be taken into account to broaden the spectrum of cover by adding agents with specific activity against resistant Gram-positive cocci (vancomycin, daptomycin).

As was mentioned above, cutaneous lesions can be secondary septic foci. This is the case in ecthyma gangrenosum, which can appear in *P. aeruginosa* infection (and can also be the primary septic focus[132]), although it has been associated with many microorganisms, both bacterial (*Staphylococcus* spp, *Corynebacterium jeikeium*, other gram-negative bacilli) and fungal (*Candida, Fusarium, Zygomycetes, Aspergillus*).

A soft-tissue infection should always be regarded as a potentially very serious clinical picture, and the possibility that it is a severe one, a necrotizing soft-tissue infection for example, should always be ruled out.[133] The difficulty of diagnosis in this setting is compounded by the relative absence of signs of inflammation accompanying neutropenia. Warning signs that should lead us to suspect a severe soft-tissue infection are how rapidly it spreads, the discordance between the symptoms and physical signs (with excessive pain or absence of pain), finding areas of necrosis, fluctuance, crepitus and hemorrhagic blisters and clinical impact. If a severe necrotizing infection is suspected, given that a large part of the pathogenesis may be toxin-mediated, it is recommended to use agents that inhibit protein synthesis and so inhibit toxin production. Clindamycin and linezolid are suitable agents and have the added advantage of offering activity against MRSA. In cases of toxic shock, intravenous immune globulin is recommended. Surgical treatment is fundamental for severe necrotizing soft-tissue infections.

The skin can also be the primary focus of fungal infection (onychomycosis in disseminated fusariosis, zygomycosis) as well as a manifestation of systemic mycosis (fusariosis). It is stressed that a biopsy of all skin lesions is essential.

Finally, the skin is the target organ of a few viral infections. In cases of vesicular lesions, treatment with acyclovir should be started once tissue samples have been taken from the ulcer bed for culture and PCR, given the possibility of reactivation of HSV or varicella zoster virus (VZV).

Intravascular catheter-related infection

Several scientific societies have developed clinical practice guidelines for the management of catheter-related infection in the general population (IDSA 2009),[134] currently being updated, SEIMC 2017,[135] and specifically for onco-hematologic patients (AGIHO-DGHO).[136] Catheter-related infection is acquired when the insertion site is colonized with infecting microorganisms or normal skin flora, via the catheter hub as a result of handling, or through hematogenous spread from a distant focus of infection. The primary mechanism of infection in central venous catheters is colonization and spread from the hub, so that the signs of infection may be absent. The microorganisms involved can be Gram-positive (*Staphylococcus* spp., *Enterococcus spp., C. jeikeium, Bacillus* spp., etc.), gram-negative (*P. aeruginosa*, *Klebsiella* spp., *Acinetobacter* spp., *S. maltophilia*, etc.) and yeasts (*Candida* spp.).

Antibiotic treatment includes a beta-lactam with antipseudomonal activity combined with an agent such as daptomycin or vancomycin with specific activity against resistant Gram-positives. Linezolid is not recommended in this situation.[137] Treatment can be adjusted once the causative agent is known. Catheter-related candidemia should be treated empirically with an echinocandin.

Paranasal sinuses

The most frequent cause of short-duration neutropenia is bacterial (including *P. aeruginosa*) and it may or may not be preceded by a viral respiratory infection. However, in patients with prolonged neutropenia, refractory febrile neutropenia, or long-term steroid treatment, the further possibility of fungal infection caused by filamentous fungi such as *Aspergillus* or *Zygomycetes* should always be considered.[138,139]

A CT scan should always be performed as a matter of urgency to assess the spread and possible bone involvement (which would suggest fungal infection), as well as an exhaustive ENT and ophthalmological exploration (look for signs of orbital cellulitis). Take biopsy samples of any

suspicious lesion for anatomopathologic examination and microbiological testing, with direct examination and cultures of bacteria and fungi. A sample of nasopharyngeal exudate should be obtained for PCR detection of respiratory viruses.

Antibiotic treatment should be started with a broad-spectrum, antipseudomonal beta-lactam with activity against Gram-positive cocci including *S. pneumoniae*, and evaluate the addition of an agent with specific activity against S. *aureus*, especially in cases of orbital cellulitis.[140] If there is any suspicion at all of fungal infection, initiate empirical antifungal treatment against the Mucorales, with high-dose amphotericin B.

Pneumonia

Pulmonary infection is one of the most difficult entities to diagnose in patients with neutropenia. In the first place, the lack of anti-inflammatory capacity means that chest X-rays (CXR) have poor sensitivity with atypical radiological patterns.[141] High-resolution computed tomography (CT) should be performed for better identification of pulmonary infiltrates. At the same time, the differential diagnosis is wide, spanning both infectious as well as non-infectious causes (heart failure, non-cardiogenic pulmonary edema in the context of regeneration syndrome or engraftment syndrome, alveolar hemorrhage, pulmonary thromboembolism, drug toxicity, GVHD, etc.). With respect to infectious causes, it is often very difficult to establish an etiologic diagnosis or to distinguish between colonization and infection, even using invasive techniques.

Community-acquired pneumonia (CAP) in the neutropenic patient should be considered a healthcare-associated infection. Bacterial causes will include those that cause CAP such as *S. pneumoniae,* atypical pathogens (*Legionella* spp., *Mycoplasma pneumoniae*), and hospital-acquired bacteria with a very high frequency of gram-negative bacilli, including *P. aeruginosa*.

Respiratory viruses (*influenza*, *parainfluenza virus*, respiratory syncytial virus, *metapneumovirus*, etc.) play a very important role in these patients, whether as the etiologic cause of the pneumonia or favoring bacterial superinfection.[142,143]

The empirical treatment should include a broad-spectrum antibacterial agent with activity against *S. pneumoniae* and *P. aeruginosa*, together with an agent (fluoroquinolones or macrolides) active against the microorganisms that cause atypical pneumonia, if it has been community-acquired.[144,145] During an influenza epidemic, initiate empirical oseltamivir until the PCR results have been obtained.[142] In patients with MRSA colonization and epidemiological settings of high endemicity, consider the addition of an active agent such as linezolid or vancomycin. Ceftaroline has bactericidal activity, although there is no experience of it in patients with neutropenia.

In critically ill patients, community-acquired pneumonia, or patients previously colonized/infected with multidrug-resistant gram-negative bacilli, it is advisable to use a dual therapy strategy, according to local epidemiology.

In cases of therapeutic failure or the appearance of respiratory symptoms during prolonged neutropenia, or disorders of neutrophil function of unspecified duration (de novo AML), the differential diagnosis should be expanded to consider infections due to filamentous fungi (*Aspergillus* spp.).[80,139.]

In patients with associated cellular immunodeficiency, the differential diagnosis will be expanded to include *Nocardia* spp., Mycobacteria spp., *P. jirovecii*, *Cryptococcus* spp. and cytomegalovirus (CMV). In risk patients with diffuse bilateral infiltrates, consider co-trimoxazole therapy or an alternative treatment regimen for *P. jirovecii* pneumonia. In risk patients, such as allogeneic hematopoietic stem cell transplant recipients or with significant alteration of cellular immunity, also consider the possibility of cytomegalovirus infection.

Urinary infection

If there is urinary infection, consider the possibility of an infection involving the parenchyma, such as pyelonephritis and prostatitis. Digital rectal examination is contraindicated.

The microorganisms involved are gram-negative bacilli and, occasionally, *Enterococcus* spp. Start treatment with a beta-lactam with antipseudomonal activity and consider adding a second antibiotic in seriously ill patients, those with indwelling urinary catheters and/or a history of MDR colonization/infection, according to local epidemiology (an aminoglycoside, glycopeptide).

CNS infection

Acute bacterial meningitis is not a common process in the neutropenic patient. The microorganisms involved include community isolates (*S. pneumoniae, Neisseria meningitidis, Haemophilus influenzae*), *L. monocytogenes,* and in neutropenic patients, gram-negative bacilli, including P. *aeruginosa*. If acute bacterial meningitis is suspected, antibiotic treatment should be started immediately after sample collection and administration of corticosteroids. Antibiotic treatment should include a high-dose beta-lactam with activity against *S. pneumoniae* and *P. aeruginosa* with good penetration into cerebrospinal fluid (cefepime or meropenem), together with ampicillin to cover *Listeria*.[146]

In the immunosuppressed patient with the clinical findings of meningitis, the possibility of cryptococcal meningoencephalitis should always be considered. Detection of cryptococcal antigen in serum and also in CSF has very high sensitivity and specificity. If it cannot be ruled out, and there is clinical suspicion in a risk patient, commence specific treatment with liposomal amphotericin B and flucytosine.[147]

If the clinical tests suggest encephalic involvement, acyclovir treatment is indicated. Also, request PCR testing of the CSF for HSV/VZV, if there is a possibility of herpes meningoencephalitis.

Given findings of space-occupying lesions of the brain, the differential diagnosis in the immunosuppressed patient is considerable and includes both infectious and non-infectious causes. Depending on the type of immunodeficiency, the infectious causes include pyogenic abscess, *Listeria, Nocardia, Cryptococcus* spp. filamentous fungi (*Aspergillus* spp. *Zygomycetes*),

toxoplasmosis, and, in our environment, *Mycobacterium tuberculosis.* Given this lengthy differential diagnosis, a biopsy of lesion tissue should be taken whenever possible, for anatomopathologic analysis and microbiological testing for bacteria, mycobacteria, fungi and parasites. Empirical use of a combination of meropenem, linezolid, co-trimoxazole and voriconazole would cover a broad spectrum. Consider empirical use of tuberculostatic drugs if there is clinical suspicion.

Table 5. Empirical antibiotic therapy according to clinical focus of infection

Entity	Antibiotic treatment	Comments
-Mild oropharyngeal mucositis	-Cefepime	
-Moderate-severe oropharyngeal mucositis	-Piperacillin-tazobactam; -Imipenem or meropenem	-If there is clinical suspicion, consider starting antiviral and/or antifungal treatment with acyclovir in patients without prophylaxis
Neutropenic enterocolitis	- Piperacillin-tazobactam; -Imipenem or meropenem	-Consider adding treatment for *Clostridium difficile* if there is a high index of suspicion
-Perianal infection	- Piperacillin-tazobactam; -Imipenem or meropenem	-Consider treatment against ampicillin-resistant enterococci (glycopeptides)
-Skin and soft tissue infection	-Cefepime - Piperacillin-tazobactam -Imipenem or meropenem +/- -Vancomycin, daptomycin or linezolid	-If there is suspicion of severe necrotizing infection, add clindamycin as a protein synthesis inhibitor -If there is a history of MRSA colonization/infection
-Intravascular catheter infection	-Cefepime - Piperacillin-tazobactam -Imipenem or meropenem + - Vancomycin or daptomycin	-Linezolid is not recommended in this setting
-Paranasal sinuses	-Cefepime - Piperacillin-tazobactam -Imipenem or meropenem	-In risk patients (prolonged neutropenia, corticosteroids), if there is the least suspicion of fungal infection, add active treatment against *Aspergillus* and the Mucorales
-Pneumonia	-Cefepime - Piperacillin-tazobactam - Imipenem or meropenem +/- -Fluoroquinolones, aminoglycosides, colistin	-Consider association with fluoroquinolones or macrolides if pneumonia is community-acquired and an atypical bacterial etiology is suspected. -In patients with MRSA colonization or an epidemiological situation of high endemicity, consider combining with linezolid or vancomycin -In severely ill patients, those previously colonized/infected with MDR gram-negative bacilli, or nosocomial cases, according to local epidemiology -During the flu season, use empirical oseltamivir until the PCR results are received -Consider the possibility of other causes (*Pneumocystis jirovecii*, cytomegalovirus) in risk patients with bilateral infiltrates
-Urinary tract infection	-Cefepime - Piperacillin-tazobactam -Imipenem or carbapenem	-Consider the addition of an aminoglycoside or glycopeptide in critically ill patients, those with indwelling urinary catheters, and/or a history of colonization/infection with multidrug-resistant microorganisms
-Acute meningitis -Meningoencephalitis	-Cefepime or meropenem + -Ampicillin + Acyclovir	-In risk patients with suggestive clinical forms, or patients with space-occupying lesions, consider other causes (*Cryptococcus*, *Listeria, Nocardia,* filamentous fungi, toxoplasmosis and *Mycobacterium tuberculosis)*

MRSA: Methicillin–resistant *Staphylococcus aureus*

4. –What is the duration of antibiotic treatment in patients with FN without clinically or microbiologically documented infection?

Search terms: "Duration OR discontinuation" AND "Neutropenia" AND "Antimicrobial OR antibiotic" AND "Therapy OR treatment".

Recommendations

1. Empirical antibiotic treatment can be stopped in hematologic patients with FN who do not have clinically or microbiologically documented infection, if they have been afebrile for at least 72 hours, and hemodynamically stable and asymptomatic since presentation, regardless of neutrophil count or expected duration of neutropenia (A-II).
2. After treatment is discontinued, the patient should be kept under close clinical observation for at least 24-48 hours, so that antibiotic treatment can be restarted early if fever returns (B-II).
3. Centers that provide antibacterial prophylaxis should consider restarting it after stopping empirical antimicrobial therapy for as long as the neutropenia lasts (C-III).

Summary of the evidence

The duration of empirical antimicrobial therapy in patients with FN of unknown origin has been the subject of controversy in recent years. The standard approach involves continuing treatment until recovery from neutropenia, especially in high-risk patients with prolonged neutropenia. This is the current recommendation of the Infectious Diseases Society of America (IDSA) in the 2010 update of their *Clinical Practice Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer.*[1] Nevertheless, the evidence that supports this recommendation, classified as B-II, is based fundamentally on one open clinical trial performed in 1979 with 33 high-risk neutropenic patients, in which discontinuation of antibiotics after 7 days of

treatment compared with maintenance until recovery from neutropenia was associated with a greater frequency of recurrent fever and mortality.[148]

The main reason for retaining this recommendation is the potential risk of recurrent fever and sepsis. Nevertheless, recurrence of fever and secondary infections are common in patients with prolonged neutropenia irrespective of whether or not antibiotic treatment is maintained.[148–150.]

In clinical practice, on the other hand, this recommendation entails extending antibiotic treatment unnecessarily in patients with prolonged chemotherapy-induced neutropenia, and conflicts with the imperative need to optimize antimicrobial treatments and, specifically, to shorten their duration.[102,151.] The selective pressure of prolonged treatment with antibiotics can lead to breakthrough infections that are difficult to treat, particularly in patients with hematologic malignancies, who are repeatedly exposed to broad-spectrum antimicrobials in prophylaxis, empirical and targeted therapy, in which multidrug-resistant bacteria constitute a serious emerging threat.[102,152,153.]

Few studies after that first one in 1979 have evaluated the early discontinuation of antibiotic therapy in adult high-risk FN patients without an etiologic diagnosis.[104,154–158.] Most of them have been non-comparative and observational in design, some with a very limited number of patients,[155–157] and have used widely varying criteria for deciding whether to discontinue antibiotic treatment (from patients with persistent fever and no established clinical infection to waiting until the patient has been apyrexial for more than 48–96 hours). Taking these limitations into account, the general conclusion of these studies is that, while early discontinuation of antibiotic treatment during neutropenia is associated with a varying amount of recurrent fever, there is no observable impact on mortality provided that antimicrobial treatment is restarted again.[104,154,155.]

In the only prospective randomized study in adult patients treated for hematologic malignancies,[104] designed to compare two empirical antimicrobial treatment regimens, the

recurrent fever and mortality rates in the 31 patients whose antibiotics were stopped after 48 hours of apyrexia were similar to those of the 29 who continued with the prescribed treatment. Some of these studies have studied the option of sequential therapy with oral fluoroquinolones until neutrophil recovery as secondary prophylaxis,[154,157,158] but none of them has so far established whether this approach successfully reduces the frequency of recurrent fever or mortality. Taking into account the rates of fluoroquinolone resistance in gram-negative bacterial isolates in blood cultures in Europe, this strategy would be feasible only in centers with low rates of resistance (less than 20%).[149,159.]

Based on the results of these studies, the most recent recommendations made by European scientific societies are disparate. The European Conference on Infections in Leukemia (ECIL) establishes (with B-II quality of evidence) that empirical antimicrobial therapy can be discontinued after at least 72 hours of intravenous therapy in patients who have been hemodynamically stable since presentation and afebrile for at least 48 h, irrespective of the neutrophil count or the expected duration of neutropenia.[97] More recently, the German Society of Hematology and Medical Oncology recommended (with B-III quality of evidence) that empirical therapy can be discontinued after at least 7 days since onset of defervescence, and only if all the signs and symptoms of infection have disappeared.[98]

A multicenter clinical trial was recently performed in Spanish hospitals[160] in 157 randomly enrolled patients with hematologic malignancies and high-risk febrile neutropenia and no etiologic diagnosis to determine the optimal duration of empirical antimicrobial treatment. In patients in the experimental group, empirical antibiotic treatment was discontinued after 72 hours of apyrexia and all signs and symptoms of clinical infection had disappeared, while those in the control group followed the standard approach of maintenance until neutrophil recovery. The results confirmed that stopping empirical antimicrobials after 72 hours of apyrexia if the patient was stable and asymptomatic successfully reduced the number of days to exposure to antimicrobials with no

impact on mortality. Furthermore, the frequency and duration of recurrent fever and the frequency of secondary infections were similar in both groups.

None of the patients with secondary bacterial infection after discontinuation of antibiotic treatment during neutropenia had a severe clinical presentation or died, which suggests that recurrent fever is not a biomarker of serious infection or mortality, and furthermore that it occurs regardless of whether or not antibiotic treatment is continued. The reduction in the number of days of antibiotic use, and hence reduced selective pressure, is an additional benefit that justifies implementation in daily clinical practice and contributes to the development of programs to optimize use of antimicrobials and limit the development of bacterial resistance in this population.

Although information on the discontinuation of antibiotics in neutropenia is more scarce in transplant recipients, one recently published retrospective study[161] analyzed the result of de-escalation of antibiotic treatment (including discontinuation with restart of quinolone prophylaxis) in 102 allogeneic HSCT recipients during the pre-engraftment period. The rates of recurrent fever and infection in the 26 patients whose followed a strategy of simplification or early discontinuation of antibiotic treatment (before 96 h) were similar to those obtained among those who never underwent de-escalation, or did so later, and no patients died. Of the 33 patients whose antibiotic treatment was discontinued at some point during neutropenia, 15% presented recurrent fever that evolved favorably with antibiotic treatment, and no patients died. The authors concluded that this approach is also feasible in allogeneic HSCT recipients with pre-engraftment neutropenia.

A recent study demonstrated that the majority (96%) of blood cultures in neutropenic patients turn positive within the first 24 h, especially those with MDR-GNB isolates. Bearing in mind that the commonest infection in neutropenic patients is bacteremia, it is advisable to reassess antibiotic treatment in patients without focality at 48 h when the microbiology results necessary to make adjustments are usually available.[162]

5. –Can patients with FN be treated with oral antibiotics? When? Which antibiotics?

Search terms: "Febrile neutropenia", "Oral treatment", "Hematological malignancies".

Recommendations

1. Patients considered to be at low risk for complications can be treated with oral antibiotics provided that they are also properly followed-up in the outpatient setting (A-II).
2. Treatment must include a fluoroquinolone with antipseudomonal activity (ciprofloxacin 750mg/12h/po) and an agent fully active against Gram-positive cocci, such as amoxicillin/clavulanic acid (875mg/8h/po), or clindamycin (300-600mg/8h po), if the patient has a proven allergy to all beta-lactams or a history of hypersensitivity (A-I). Another alternative is a combination of ciprofloxacin with cefixime or cefuroxime (A-II).
3. Other oral regimens including levofloxacin or ciprofloxacin in monotherapy have been studied less (B-III).
4. Fluoroquinolones should not be used as initial empirical treatment in patients who have received them as prophylaxis. (A-III).
5. Any patient, whether in the emergency room or after admission, who presents signs and symptoms of hemodynamic instability, focality, oral intolerance, new clinical signs and symptoms, or microbiological species not susceptible to initial empirical therapy are isolated, should be admitted to hospital or continue as an inpatient in order to expand the tests for fever syndrome and modify empirical treatment according to the protocol for high-risk patients (A-III).

Summary of evidence

In general, patients can be divided into two groups based on their risk of infectious complications (high-risk and low-risk), taking into account the type and condition of the underlying hematologic disease, the chemotherapy dose intensity of received and the characteristics of the patient.

The objective of patient stratification is to predict the individual risk of developing complications associated with the infection and hence to determine the need for hospital admission and monitoring and parenteral antibiotic administration, or whether it is possible to provide oral treatment in the outpatient setting together with close follow-up. It should at the same time be borne in mind that the risk stratification models commonly used in cancer patients (Talcott, MASCC) may not apply to patients with hematologic malignancies because of their particular characteristics.

Oral antibiotics can be administered to patients with FN, provided that they belong to the subset of low-risk patients. In this case, they would be possible candidates for dual oral antibiotic therapy and outpatient management, thus reducing toxicity, iatrogenesis, and the number and duration of hospital admissions.[1,4,163–166.]

For patients with proven allergies to all beta-lactams or a history of hypersensitivity, use of ciprofloxacin or clindamycin is recommended. Bearing in mind that some patients with penicillin allergy can tolerate cephalosporins and that the prevalence of quinolone resistance in Enterobacteriaceae in our environment is at present around 20–30%, an alternative is a cephalosporin (cefixime or cefuroxime) plus ciprofloxacin in combination.[167]

The criteria for a low-risk episode include the following:

Criteria for exclusion:

- Patients undergoing allogeneic stem cell transplantation or intensive chemotherapy treatments, for example: those receiving intensive induction chemotherapy or high-dose cytarabine (ara-C) or similar as consolidation treatment for acute myeloid leukemia, or receiving DT-PACE chemotherapy for plasma cell leukemia, or BURKIMAB, DA-EPOCH level ≥3 or Hyper-CVAD chemotherapy for lymphoma, among others.

- Acute organ dysfunction (clinically significant gastrointestinal symptoms, bleeding, oliguria, development of new pulmonary infiltrates, hypoxemia, or the appearance of new neurological symptoms).
- Clinically significant comorbidities including pulmonary disease, hepatic or renal dysfunction or any clinically relevant worsening.
- Clinically significant cellulitis.
- Central venous catheter infection.
- Previous colonization/infection with MDR bacteria
- Quinolone prophylaxis or previous infection due to fluoroquinolone- or β-lactam-resistant gram-negative bacteria.[4]
- Recently admitted to intensive care.

Ensure [4,163–165]:

- Hemodynamic stability
- Able to tolerate oral medications.
- Very good social and environmental conditions for outpatient management of the episode.

It is absolutely essential to know the local antibiotic susceptibility patterns of the main microorganisms to the antibiotics that will be used.

Before discharge, it should be ensured that there is proper outpatient control. This includes the possibility of the patient being able to reach the hospital in 1.5 hours or less at any time of day or night if there is persistent or recurrent fever, oral intolerance, any new signs and symptoms or clinical worsening, and also that there is adequate family support or a carer available, and no previous history of failure to comply with treatment or visits. The possibility of daily monitoring of temperature, together with a commitment to comply with visits and frequent analytical controls should also be ensured. [4,42,165].

At 48-72 h, the clinical progress of the patient (apyrexia) and the results of microbiological tests should always be re-evaluated. If fever persists despite appropriate treatment, the patient should be admitted to hospital to test for and treat any new infection or for the progression of the previous one. [1,163–165].

6. – When is empirical antifungal treatment indicated in a patient with NF?

Search terms: "Febrile neutropenia AND empirical antifungal treatment". "Febrile neutropenia AND pre-emptive antifungal therapy OR diagnostic-driven approach".

Recommendations:

1. High-risk neutropenia patients not receiving prophylaxis against filamentous fungi can be given empirical antifungal treatment if fever with no other obvious cause persists after 4-5 days of broad-spectrum antibiotics and hemodynamic instability (B-II).
2. Alternative treatment strategies, such as biomarker-guided treatment using galactomannan (GM) or beta-D-glucan (BDG), reduce the use of antifungals safely and without affecting mortality in neutropenic patients (A-I).
3. Empirical antifungal treatment is not recommended in the vast majority of hematologic patients with high-grade neutropenia who receive antifungal prophylaxis covering filamentous fungi (A-II).

Summary of the evidence

Empirical antifungal treatment is administered to high-risk patients with persistent or recurrent fever with no obvious cause after 4–7 days of broad-spectrum antibiotics and neutropenia is expected to continue for >7 days [42] This treatment strategy was proposed in the 1980s as a way of guaranteeing early antifungal therapy in patients who might have fungal infection. Nevertheless, despite the rapid and widespread acceptance of this strategy, the clinical

evidence supporting empirical antifungal treatment as beneficial for the patient is unclear, and several studies have not shown any benefits.[168]

In the present era, the concept of empirical antifungal therapy has to contend with various conflicting issues. First, according to this strategy, between 30 and 50% of patients with prolonged neutropenia ought to receive antifungal treatment. Yet the incidence of invasive fungal infection in the subset of patients at highest risk would only be about 10% of patients.[169] Second, improvements in techniques for diagnosing fungal infection mean that more patients can be diagnosed and earlier.[170] Third, the strategy of preemptive treatment reduces use of antifungals safely without affecting mortality in neutropenic patients.[171,172.] Lastly, empirical treatments are more expensive in economic terms and involve more adverse effects.[173]

At the same time, the incidence of breakthrough fungal infection in patients who receive antifungal prophylaxis against filamentous fungi is close to 3%.[174,175] The role that empirical antifungal treatment can play in this setting is even more difficult to establish, since persistent fever in these patients is not often associated with fungal infection,[176] In this scenario therefore empirical antifungal therapy seems somewhat inappropriate. It is recommended to carefully rule out other possible causes of fever. Although there is at present no scientific evidence, the latest published guidelines on aspergillosis suggest that if the patient presents with more than 10 days of fever without any other obvious cause and is not hemodynamically stable, consider instituting empirical antifungal treatment.[177] The common sense recommendation is to change the family of antifungal agent administered as prophylaxis.

TARGETED ANTIBIOTIC TREATMENT

1. – In documented cases of microbiological isolates, can antibiotic treatment be adjusted to the susceptibility of the microorganism identified, even if neutropenia persists?

Search terms: "targeted OR de-escalation" AND "therapy OR treatment" AND "febrile neutropenia" AND "antimicrobial OR antibiotic".

Recommendations:

1. In patients with documented microbiological isolates, treatment should be targeted at the isolate, taking into account its in vitro activity (including MIC), pharmacokinetic/ pharmacodynamic properties, as well as the individual characteristics of the patient (A-I).
2. If the microorganism isolated is considered to be the only causative agent of the febrile episode, it is preferable to use an antimicrobial, normally a beta-lactam, with a narrower spectrum when active (B-III).
3. Beta-lactam monotherapy is appropriate for targeted treatment of most cases of gram-negative bacteremia (A-I).

Summary of the evidence

After empirical antimicrobial therapy has started, patient response should be closely monitored with daily clinical assessments, bearing in mind that the mean time for defervescence in febrile neutropenic patients with hematological malignancies can be up to 5 days.[103] Modification of the initial empirical antimicrobial regimen in these patients should be guided by their clinical development and the results of microbiological tests carried out, and not only by persistence of fever. [42,97,153,163]

In patients with documented microbiological isolates thought to be the cause of the fever, treatment should be targeted at the pathogen once the patient is stable and *in vitro* susceptibility test results are available. When it comes to selecting the antimicrobial of choice, factors to be taken into account include: its *in vitro* activity, including minimum inhibitory concentration (MIC) when it is available, the pharmacokinetic and pharmacodynamic properties of the antimicrobial, possible drug interactions with other medications such as immunosuppressants, and the

individual circumstances of the patient. The final choice from all the options available should be the antibiotic with the narrowest spectrum possible when active *in vitro* in order to avoid unnecessary antibiotic pressure, provided that the isolated microorganism (generally in blood culture) is considered to be the sole cause of infection.[42,97,163.] In a recent study evaluating the result of simplified antibiotic treatment in allogeneic HSCT recipients (in the pre-engraftment phase) with FN and bacteremia, 17.5% (10 of 74) of patients had recurrent fever, none died and all progressed favorably.[161]

Various meta-analyses and randomized controlled trials have not shown that combination treatment (empirical or targeted) with aminoglycosides reduces overall mortality in hematologic patients with FN,[113,178,179] although most of these studies were conducted before antibiotic-resistant bacteria became a major problem in the treatment of infection in patients with hematologic malignancies. On the other hand, combination treatment for bacteremia caused by gram-negative bacteria in the first 24-48 hours, before *in vitro* susceptibility is known, increases the likelihood that the isolate will be susceptible to at least one of the antimicrobials used, which has been associated with lower mortality.[180]

Taking both these factors into consideration, de-escalation to beta-lactam monotherapy, following the criteria mentioned previously, is appropriate in most cases for patients who present bacteremia caused by gram-negative bacteria and have received initial combination treatment with aminoglycosides or fluoroquinolones, until definitive identification and *in vitro* susceptibility results are available.[113,178,179] Nevertheless, combination treatment based on *in vitro* susceptibility tests may be necessary for targeted treatment of infections caused by certain resistant gram-negative bacteria, such as carbapenemase-producing Enterobacteriaceae or extensively drug-resistant (XDR) *P. aeruginosa.* For optimal selection of targeted therapy, especially in cases with MDR bacteria, collaboration between hematologists, infectious diseases specialists and

microbiologists is crucial, since many therapeutic options have not been properly evaluated specifically in hematology patients.[97]

2. – What is the duration of antibiotic treatment in patients with FN and clinically or microbiologically documented infection?

Search terms: "duration OR discontinuation" AND "neutropenia" AND "antimicrobial OR antibiotic" AND "therapy OR treatment".

Recommendations:

1. In hematologic patients with FN and clinically documented infection, antibiotic treatment can be discontinued when the clinical signs and symptoms of infection have resolved and the patient has been afebrile for at least 72 hours. (B-II).
2. In hematologic patients with FN and microbiologically documented infection, treatment should be maintained until clinical and microbiological cure of infection (resolution of signs and symptoms of infection and microbiological eradication), and after at least 4 days of apyrexia and a minimum of 7 days of antibiotic treatment (B-III).
3. In both situations, if neutropenia persists after treatment has been discontinued the patient should be kept under close clinical observation for at least 24-48 hours, so that antibiotic treatment can be restarted promptly if fever recurs (B-II).
4. Centers that give prophylactic antibacterial agents should consider renewing this regimen when empirical antibiotics have been discontinued for as long as the neutropenia continues (C-III).

Summary of evidence

As was the case with unexplained fever, the standard recommendation for duration of therapy in patients with clinically or microbiologically documented infection has, for many years,

been to continue with antibiotic treatment until neutrophil recovery, independently of clinical resolution of infection. This recommendation is based on the effectiveness and safety of this strategy after many years of experience. [42,163]

There are no published studies that have been designed specifically to define the optimal length of treatment in adult hematology patients with febrile neutropenia and microbiological documentation. Most studies, including clinical trials comparing different regimens of empirical antibiotic therapy in FN, establish a minimum of 7 days of targeted therapy for microbiologically or clinically documented infections, and for the patient to be afebrile on at least four of those days.[105,181–184.] In general, these studies exclude patients with initial severity of clinical presentation, central nervous system infections or pulmonary infiltrates. On the other hand, as described in the section on empirical antibiotic treatment for fever of unknown origin, various prospective and retrospective observational studies performed on adults with high-risk febrile neutropenia have demonstrated that discontinuation of antibiotic treatment in patients with prolonged neutropenia is not associated with increased mortality, although it is associated with recurrence of fever in a variable number of patients. [104,154–158.]

Based on evidence provided by studies specifically designed to evaluate early discontinuation of antimicrobials, as well as what can be inferred about duration of antibiotic treatment from clinical trials designed to compare different antibiotic regimens for FN in patients with hematologic malignancies, the latest recommendations of the ECIL[97,163] propose not making neutrophil recovery the necessary precondition for determining length of antibiotic treatment in patients with microbiologically or clinically documented infection. Hence, the recommendation for patients with febrile neutropenia and microbiologically documented infection is that antibiotic treatment can be discontinued after at least 7 days of treatment and 4 days of apyrexia, provided that all signs and symptoms of infection have resolved, regardless of the persistence of neutropenia.[3]

In patients with clinically documented infection, the recommendation is to consider discontinuation of treatment after 72 hours if the patient has been hemodynamically stable since presentation and afebrile for at least 48 hours, and there is complete resolution of the signs and symptoms of infection. This recommendation moreover takes into consideration the need to reduce the length of antimicrobial treatment to avoid collateral damage, which is part of the optimization strategy required to combat emerging antibiotic resistance.

One recent multicenter randomized controlled trial, designed to optimize the duration of antibiotic treatment in patients with hematological malignancies and FN, included patients with clinically documented infection but no microbiological diagnosis.[160] Mortality in patients whose antibiotics were discontinued after at least 72 hours of apyrexia and the same of clinical recovery was similar to that in patients who also waited until recovery from neutropenia before stopping treatment, without higher rates of recurrence of fever or secondary infections. That randomized trial did not stipulate a minimum duration of antibiotic treatment,[160] although cure of infection was ensured with a rigorous clinical assessment of resolution of signs and symptoms of infection, control of focal infection, if applicable, and negative blood cultures (initial or successive)

3. – When is removal of a central venous catheter indicated?

Search terms: “central venous catheter removal”, “catheter-related infection”, “management of central venous catheter infection” “catheter-related bloodstream infection”.

Recommendations:

1. When CVC infection is documented, consider removal of the catheter wherever possible,, weighing up the advantages of removal against the difficulty of obtaining new venous access (A-II).
2. It is recommended to remove the CVC when there is documented catheter-related bloodstream infection (CRBSI) and local signs at the insertion site (suppuration), along

the tunnel tract (tunnel infection), or if the patient presents criteria for severe sepsis with hemodynamic instability (septic shock) (AII).

3. To improve the prognosis of the patient, it is recommended to remove the CVC when there is documented CRBSI due to fungi (normally *Candida* spp), *S. aureus*, enterococci, gram-negative bacilli (especially *P. aeruginosa*) and mycobacteria (A-II). Removal is also recommended in infections with associated bacteremia caused by microorganisms that are difficult to eradicate (*Bacillus* spp., *Micrococcus* spp. and *Propionibacterium* spp.) (B-II).
4. In uncomplicated infections or where bacteremia is caused by microorganisms different from those mentioned above, systemic targeted antibiotic treatment can be applied without removing the CVC and antibiotic lock therapy should be considered (B-II).
5. Removal of the CVC is recommended if persistent bacteremia is detected (evidenced in positive follow-up control cultures) 48h-72h after starting targeted antibiotic treatment (A-II), if there is no other obvious clinical focus (B-II), if there is infective endocarditis or peripheral embolism (A-II) or an early relapse due to the same microorganism after completion of antibiotic treatment, or failure of conservative treatment (B-II).
6. If fever persists in a neutropenic patient with an indwelling catheter after other focalities have been ruled out, but catheter-related infection has not been confirmed, consider removal of the catheter if there is sepsis or local erythema in the pericatheter area (B-II), or if fever persists and there is no other possible cause despite the absence of sepsis or local signs of infection (C-III).

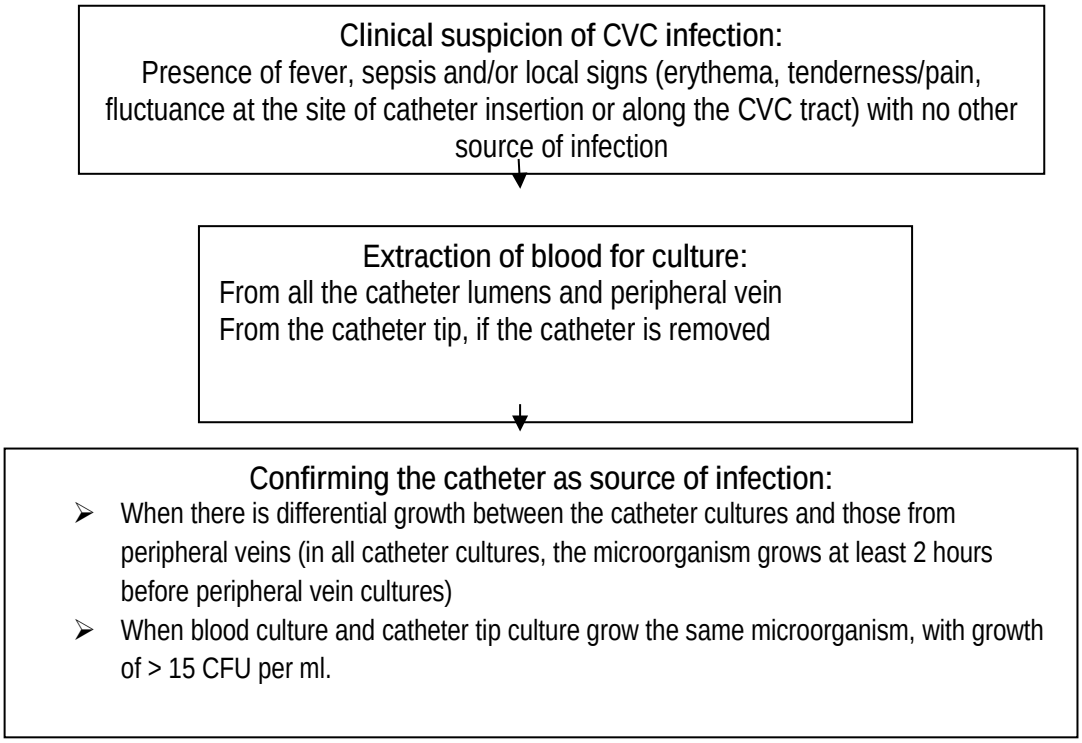
Summary of evidence

Most patients diagnosed with hematologic malignancies who receive intensive chemotherapy, as well as recipients of hematopoietic stem cell transplants, require central

venous access for treatment. There are different types of central venous access depending on the individual needs of the patient, for both long-term (permanent tunneled CVCs, catheters with subcutaneous reservoirs) and short-term use (centrally or peripherally inserted CVCs of up to 30 days, although many patients with short-term CVCs use them for more than 30 days, depending on their needs). In this document, given that most of the recommendations for removal of a CVC refer to the clinical situation of the patient, whether or not there are localized manifestations of infection, and the type of causative microorganism, no reference is made to different management by type of CVC (long- or short-term), except in specific situations that are detailed as and when necessary.

Catheter-related infection (CVC infection) is a common complication in patients with hematologic malignancies. Correct diagnosis and confirmation of catheter-related infection in these patients is the first challenge that the physician faces and is essential for proper management of the infection and the CVC. We recommend following the diagnostic criteria for CVC-related infections proposed by the CDC and IDSA scientific societies, which are the ones most used in daily practice, and which also share the definition used in the ECIL guidelines. These are summarized in figure 3 (adapted from *Zakhour R et al.*).[185]

Figure 4. Diagnostic criteria of CVC-associated infection (adapted from *Zakhour R et al,*[185]*).*



Given that the hematologic patient with neutropenia is already frail and that any infection with a specific localized focus can, despite antibiotic treatment, trigger severe life-threatening sepsis, it seems natural to assume that the infection will resolve earlier by removing the source of infection (in this case the CVC). When a diagnosis of catheter-related infection is made, we should consider whether or not it is possible to remove the CVC with reference to the needs of the patient, the variety of intravenous treatments required and the difficulties associated with venous access. In principle, whenever possible, the infected CVC (which is used to administer medication and is therefore constantly being handled) should be removed, especially if there is catheter-related bloodstream infection and/or symptoms of severity. In some cases, it is recommended to remove the catheter immediately in order to: a) improve the prognosis of the patient (those with sepsis or septic shock, for example);[134,186–188] b) to avoid antibiotic treatment failure (when there are signs of local infection, or along the tunnel tract, or of thrombosis associated with possible microbial attachment to the CVC surface); and c) to avoid endovascular

complications or septic embolism associated with microorganisms such as *S. aureus* or *Candida.*[134,186,189–192] Although some studies have debated whether the early removal of a CVC in candidemia is useful,[189] if the catheter is the source of the candidemia, removal is recommended in neutropenic patients.

When certain microorganisms are isolated in culture (*S. aureus*, *Candida*, enterococci, gram-negative bacilli, mycobacteria), early removal is recommended as soon as the causative agent is known in order to improve the prognosis of the patient (because of their ability, whether biofilm-mediated or not, to attach to CVC surfaces, and their capacity for septic emboli). On this point, depending on the isolate, the IDSA makes the following specific recommendations: if the CVC is short-term, it is recommended to remove the CVC if the infection is caused by gram-negative bacilli (in general)*, S. aureus,* fungi, enterococci and mycobacteria. If the CVC is long-term, it should be removed when there is evidence of *S. aureus, P. aeruginosa,* fungal or mycobacterial infection.

In catheter-related infection due to microorganisms other than *S. aureus*, enterococci, gram-negative bacilli (*P. aeruginosa* in long-term CVCs), *Candida spp*, mycobacteria, catheter removal is recommended in order to reduce the risk of relapse of infection in certain situations:[193–195] complicated infections (endovascular infections), persistent bacteremia and "breakthrough bacteremia" (repeated positive control cultures or appears after targeted antibiotic therapy) or septic emboli appear. Likewise, removal of the CVC (both long-term and short-term) is recommended in uncomplicated infections and bacteremia caused by microorganisms that are less virulent than those described above but are difficult to combat, such as *Bacillus* spp*., Micrococcus spp.* or *Propionibacterium* spp. Outside of these settings, use of antibiotic lock therapy is a possibility, together with systemic antibiotic treatment targeting the specific isolate (B-II), especially in patients with long-term indwelling catheters with difficulties of venous access who present uncomplicated infections caused by less virulent, susceptible bacteria.

In patients whose characteristics would make it difficult to remove the CVC, a possible option would be CVC exchange over the guidewire.[196] In such cases, it is recommended to use lines coated with antibiotics.

In patients with fever and bacteremia and an indwelling CVC that has not been confirmed as the direct source of infection although there is a possible causal relationship (for example, the microorganism isolated in the blood culture is a skin colonizer, or the patient has fever and cultures have yielded some microorganism and no other focality is possible), in such cases, the bacteremia is not catheter infection-related and removal is not recommended, although the evolution of the patients should be closely monitored.

TREATMENT OF MULTIDRUG-RESISTANT GRAM-NEGATIVE BACILLI (MDR-GNB)

The rapid expansion of bacterial resistance poses a major threat and has become a priority public health issue, making it essential to reconsider traditional approaches to the treatment of infection. In this scenario, it is necessary to guarantee not only that treatment is effective, but also that rational use is made of antimicrobials, especially those that are used as drugs of last resort (such as carbapenems and the new beta-lactams), which are at risk of running out. Our objective in these guidelines is not to provide an exhaustive description of all the therapeutic treatment options in the complicated setting of multidrug-resistant gram-negative bacilli (MDR-GNB), which can be consulted in other specific documents,[197,198] but to define those that are currently considered as treatments of choice. Unfortunately, there are hardly any studies in neutropenic patients, who are represented with variable results in the different cohort studies published. For this reason, it has been necessary to extrapolate most of the recommendations from studies carried out in the general population until such time as better evidence is available.

TREATMENT OF INFECTIONS CAUSED BY MULTIDRUG-RESISTANT GRAM-NEGATIVE BACILLI (MDR-GNB).

1. – What is the treatment of choice for cephalosporin-resistant Enterobacteriaceae?

Search terms: "(ESBL or *extended-spectrum beta-lactamase*) and treatment and outcome"; "AmpC and *Enterobacter** and treatment and outcome".

Recommendations:

1.1 Targeted therapy in infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae.

1.1.1 In stable patients, the targeted therapy of choice against extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae is a beta-lactam/beta-lactamase inhibitor (BLBLI) combination, provided that in vitro susceptibility is shown (B-II).

1.1.2 Use of carbapenems is recommended for patients with sepsis or septic shock criteria (C-I).

1.1.3 Piperacillin-tazobactam and meropenem should be administered in extended infusion, since this has been shown to improve prognosis in severe infections, compared with short-term infusions (A-I).

1.1.4 Piperacillin-tazobactam should be avoided for treating high-inoculum infections caused by strains with MIC ≥ 4 mg/L (B-II).

Summary of evidence

ESBLs are enzymes that are able to hydrolyze most penicillins and cephalosporins (except for cephamycins) and are inhibited by beta-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam, avibactam).[199] The BLBLIs amoxicillin-clavulanic acid or piperacillin-tazobactam are proposed as therapeutic options therefore since they are theoretically capable of inhibiting this resistance mechanism, although there is as yet very little accumulated experience of ceftazidime-avibactam and ceftolozane-tazobactam. The traditional recommendation of using carbapenems stems from observational studies that described higher survival rates in groups of

patients treated with carbapenems as compared with other antimicrobials. Nonetheless, in many of these studies, the antibiotics used as comparators were fluoroquinolones, cephalosporins, and aminoglycosides,[200] which are not appropriate antibiotics for most infections caused by ESBL-producing Enterobacteriaceae, generally because of co-resistance. Many recent, well-designed multicenter observational studies have evaluated this question, most of which compared the efficacy of carbapenems versus BLBLIs and found no differences between the two groups. [200–205.] One of these studies was performed specifically in neutropenic patients, with no differences in prognosis between the two groups, although in this case, the number of patients treated with BLBLIs was limited.[206]

The only observational studies that showed a worse prognosis in patients treated with piperacillin-tazobactam versus carbapenems were those published by Tamma et al. and Ofer-Friedman et al.[207,208.] Both studies included predominantly patients with high-inoculum infections (pneumonia, intraabdominal infections etc.) due to strains of ESBL-producing Enterobacteriaceae with higher piperacillin-tazobactam MICs (>=4 mg/L). This value is one and two dilutions, respectively, below the susceptibility cut-offs established by EUCAST and CLSI. Hence, strains reported as susceptible may not respond to conventional treatment, which is why it is important to consider MIC values.[209] Furthermore, in the study by Tamma et al., the piperacillin-tazobactam dosage (60% of patients were administered 3.5 g every 6 hours in short infusion) suggests under-dosing, and the study by Ofer-Friedman et al. did not specify the doses used. *In vitro* and *in vivo* studies conducted show that piperacillin-tazobactam can be affected by the so-called inoculum effect,[210,211] which means that its efficacy could be compromised in high-inoculum infections caused by strains showing higher MICs, as was observed subsequently in a few clinical studies.[207,208,212] In these settings, therefore, it is recommended to use piperacillin-tazobactam with caution. It should also be underlined that this effect has not been described for amoxicillin-clavulanic acid.[210,211]

The first non-inferiority clinical trial was recently published, which compared treatment with meropenem versus piperacillin-tazobactam in patients with bloodstream infections caused by cephalosporin-resistant Enterobacteriaceae.[213] The trial was interrupted early when higher 30-day crude mortality was detected in patients treated with piperacillin-tazobactam. Nevertheless, none of the deaths recorded was associated either with the infection or the study drug, but were due fundamentally to non-infectious complications in patients with advanced cancer, variables which, among other things, were not properly controlled for in the post hoc tests carried out with multivariate analysis. It is difficult therefore to infer from these results that carbapenem use would translate into reduced mortality in this sample. The rest of the secondary variables showed discrepant results: no significant differences were detected in the days before resolution of symptoms or in the microbiological cure rates, yet the 5% non-inferiority margin for the "clinical and microbiological" cure variable on day 4 of treatment was not met. Once again, the results do not allow us to draw definitive conclusions, because the confidence interval for this variable also included the null effect value, and also because there were circumstances in the piperacillin-tazobactam arm that determined a slower response (a higher rate of high-inoculum infections, more patients with sepsis, administration of the drug in short infusion, MIC90 values of isolates close to the cut-offs of susceptibility to piperacillin-tazobactam, etc.). In our opinion, the major limitations of this study, when set against the whole body of previous evidence supporting the use of BLBLIs, do not justify the overall ecologic cost that would be incurred by using carbapenems for all infections caused by cephalosporin-resistant Enterobacteriaceae.

Hence, until better evidence is available, we recommend reserving carbapenems for neutropenic patients with sepsis and for high-inoculum infections caused by strains showing higher MICs for BLBLIs, as detailed in the recommendations above.

In cases where piperacillin-tazobactam or meropenem is indicated, it is advisable to administer these in extended infusion. Multiple randomized trials have demonstrated that this

dosing strategy improves the prognosis of patients with severe infections.[214] Only one of these trials has been carried out specifically in neutropenic patients and showed the same results.[215]

1.2. Targeted treatment of infections caused by AmpC-producing Enterobacteriaceae

1.2.1 Cefepime and fluoroquinolones are the preferred treatment options for infections due to AmpC-producing Enterobacteriaceae susceptible to these antimicrobials (B-II).

1.2.2 Piperacillin-tazobactam is a valid therapeutic option if in vitro activity is shown (B-II), but should be avoided for treating high-inoculum infections caused by AmpC-producing Enterobacteriaceae with MIC ≥ 4 mg/L ((B- III).

1.2.3 Use of carbapenems is recommended for patients without alternative treatment options, or with sepsis or septic shock criteria (C-I).

1.2.4 We recommend that piperacillin-tazobactam, cefepime and meropenem be administered in extended infusion, since this has been shown to improve the prognosis in severe infections when compared with short-term infusions (A-I).

Summary of the evidence

AmpC beta-lactamases are molecular class C enzymes able to hydrolyze penicillins, monobactams and cephalosporins (except for cefepìme) and are not well inhibited by the classic ESBL inhibitors, especially clavulanic acid and sulbactam.[199] Avibactam, apart from inhibiting class A beta-lactamases (ESBLs and KPC-type carbapenemases) and some from class D (OXA-48), also inhibits class C beta-lactamases. The latter are chromosomally encoded and are of great importance in *Enterobacter* spp., *Serratia marcescens*, *Citrobacter freundii*, *Providencia* spp. and *Morganella morganii* (sometimes known as the 'ESCPM' group). AmpC hyperproduction

generates resistance to third-generation cephalosporins, although MIC values for cefepime are still within the susceptible range. As a result of transmissible plasmids acquiring the genes responsible for AmpC beta-lactamase (pAmpC), these enzymes are also present in *E. coli* and *K. pneumoniae*. With some exceptions (for example, the DHA enzyme), they lose inducibility and confer a resistance profile that is similar to chromosomal hyperproduction, but with MIC values for cefepime in the resistance range.

The presence of chromosomal AmpC genes belonging to the "ESCPM" group may be the reason why, in serious infections, initial *in vitro* susceptibility to certain antibiotics is compromised during treatment, owing to the derepression of AmpC induced by antibiotic pressure.[216] Given that this mechanism can confer resistance to practically all cephalosporins and BLBLIs, there has been a tendency to avoid these antibiotic families to treat this type of infection and to prioritize the use of carbapenems.[217] Nevertheless, cefepime and fluoroquinolones are not substrates for this type of beta-lactamase, and piperacillin-tazobactam is a weak inducer of AmpC,[216] so that these options would be potentially valid if they are included as active in the antibiogram.

The MERINO trial mentioned above included only 10% of infections that were due to AmpC-producing Enterobacteriaceae, which, together with the methodological limitations already outlined, prevents us from drawing conclusions that extrapolate to this type of patient. The observational studies designed to define optimal treatments for infections caused by AmpC-producing Enterobacteriaceae[213] are less numerous and more disparate than those published on ESBL-producing Enterobacteriaceae,[218–224] and none was conducted specifically with neutropenic patients. Nevertheless, none of these studies showed a better prognosis in the group of patients treated with carbapenems versus any of the comparators, nor after an aggregated analysis in a recent meta-analysis.[225] The specific experience that has been collected does not allow us to draw firm conclusions in the case of the AmpC-type beta-lactamases (pAmpC).[226]

It has already been mentioned that it is advisable to use piperacillin-tazobactam with

caution in high-inoculum infections (such as pneumonia, complicated intraabdominal infections and so on) caused by strains with higher MICs (>=4 mg/L). Although the clinical impact of this effect has not been demonstrated in studies of infections due to AmpC-producing Enterobacteriaceae, the results observed in infections due to ESBL-producing Enterobacteriaceae[207,208,212] make it advisable to exercise similar caution when using piperacillin-tazobactam in this other scenario until there are clinical trials available to resolve the question,[227] especially when treating patients with neutropenia.[228]

Everything that has been reported in connection with carbapenems in the studies available,[221–223,225] applies equally to the outcome of infections due to AmpC-producing Enterobacteriaceae treated with cefepime, provided that the etiologic agent shows susceptibility. Centers that use CLSI recommendations[229] for susceptibility reporting should bear in mind that treatment with cefepime against Enterobacteriaceae with MICs>=2 mg/L (categorized as 'susceptible dose dependent') has been associated with higher failure rates.[230,231.] This consideration is irrelevant with the EUCAST recommendations,[199] since strains categorized as 'susceptible' have a cefepime MIC<=1 mg/L. In summary, due to the limitations of the available evidence,[225] and until appropriate clinical trials are available,[227] we continue to consider it advisable to use carbapenems in more seriously ill patients.

2. – What is the treatment of choice for carbapenem-resistant gram-negative bacilli?

2.1 Targeted therapy of infections caused by carbapenem-resistant Enterobacteriaceae (CRE).

Search terms: "(carbapenemase or KPC or OXA or NDM or VIM) and treatment and outcome".

Recommendations:

2.1.1 Severe infections caused by KPC-producing Enterobacteriaceae in neutropenic patients should be treated with a combination of at least two

active drugs from the options included in the antibiogram (meropenem, colistin, tigecycline, fosfomycin and aminoglycosides) (B-II). We recommend the same approach for treating severe infections caused by other carbapenemase-producing Enterobacteriaceae (CRE) (C-III).

2.1.2 For infections due to strains with meropenem MICs < 16 mg/L, the combination regimen should include high-dose meropenem (2g every 8 hours) in extended infusion (over 3 hours) (B-II)

2.1.3 Ceftazidime-avibactam may be an alternative for severe infections due to KPC-producing or OXA-48-producing Enterobacteriaceae (C-III). We do not have well-designed comparative studies available that enable this drug to be positioned against other treatment options (undecided). Nor are there data to support its use in combination therapy (undecided).

2.1.4 In this type of infection, it is especially important to ensure control of the source of infection and to administer high-dose antibiotics with optimized dosage regimens, monitoring plasma levels whenever possible (table 4) (B-II).

Summary of the evidence

Carbapenem resistance in Enterobacteriaceae can be explained in the majority of cases as due to the acquisition of carbapenemases, beta-lactamases that confer resistance to almost all beta-lactams.[199] No clinical trials have determined the best treatment for these infections, and the available evidence comes from observational studies. Colistin, fosfomycin, tigecycline, the aminoglycosides and meropenem show varying degrees of *in vitro* activity against different isolates of CRE,[232] but these options have been associated with less efficacy.[233–236] Various publications have shown that prognosis is better when at least two active drugs are

combined,[237–243] although this is not the case according to other authors.[244,245.] In a sensitivity analysis of an extensive multinational cohort, Gutiérrez-Gutiérrez *et al*. showed that the benefit of combination treatment was limited to patients at increased risk of mortality, whereas in less serious infections, monotherapy obtained comparable results to combination regimens.[237] The mortality rate for CRE infections in neutropenic patients has been situated at above 40%,[246,247] which makes this a high-risk population. Although very few studies, and all of them observational, have evaluated combination treatment in hematologic patients, all have reported that the use of combinations was beneficial.[25,26.]

No clinical trials have evaluated which is the best combination of antimicrobials, although observational studies published describe better outcomes with those that include meropenem if the MIC is <16 mg/L and administration is optimized (2 g every 8 hours in extended 3-hour infusion) to give better microbial exposure to the antimicrobial agent.[235,240,248,249.]

The impact of colistin resistance as a result of the emergence of the *mcr-1* gene (and its variants) or its clinical impact has not yet been evaluated in any depth,[250] although it is advisable, as with chromosomal colistin resistance,[251] to avoid its use, since such strains are categorized as resistant in antibiograms.

The recently commercialized drug, ceftazidime-avibactam, shows activity against KPC- and OXA-48-producing Enterobacteriaceae , although not against other metallo-β-lactamase-type carbapenemases. Clinical experience in this setting is limited to series with a small number of cases,[252–256] one of which included exclusively hematologic patients.[254] These studies show variable mortality rates, ranging from 8% to 39.5%,[252–256] and some of them have reported a considerable number of recurrent infections and cases of ceftazidime-avibactam resistance during treatment.[256,257] Only one retrospective study has analyzed the potential advantages of this antibiotic against the classic combination regimens, and better results were observed in patients who received ceftazidime-avibactam. Nonetheless, the number of patients treated with

the drug was very small (13 cases) and more than a half (61%, 8/13) had low-risk foci, which limits the external validity of the results.[253] Another retrospective study compared the efficacy of ceftazidime-avibactam versus colistin in the treatment of CRE infections, and showed a considerable difference in 30-day mortality (9% vs. 32%).[255] Nevertheless, the limited number of patients who received ceftazidime-avibactam (n=38), the heterogeneous nature of the groups compared (those who received colistin were largely critically-ill patients) and the lack of data about dosing in the colistin group mean that the conclusions of the study should be interpreted with caution.

Hence, while ceftazidime-avibactam may be an effective therapeutic alternative, the scant clinical experience and the absence of well-designed comparative studies mean that it cannot be positioned alongside the traditional combination therapy regimens. The choice should be based on the individual characteristics of the patient, the local epidemiology of resistance and local antimicrobial stewardship policies. No study of combination therapy has included patients treated with ceftazidime-avibactam, so that the usefulness of this antimicrobial agent is yet to be defined.

The recommended dosages for all these drugs are detailed in Table 6.

2.2. Targeted therapy of extensively drug-resistant (XDR) and pandrug-resistant (PDR) non-fermenting gram-negative bacilli (NFGNB).

Search terms: BGN-NF XDR and PDR: (*Acinetobacter* or *Pseudomonas*) and (resistant or resistance or MDR or XDR or PDR) and treatment and outcome.

Recommendations:

2.2.1 In the case of XDR NFGNB infections for which there is a fully active therapeutic alternative, single-agent treatment is recommended with optimized administration (B-I), prioritizing the use (in the following order) of beta-lactams, sulbactam (in

infections due to *A. baumannii*) and colistin, provided that *in vitro* susceptibility is shown (C-II). Avoid monotherapy with aminoglycosides or tigecycline for the treatment of severe infections (A-II, A-I).

2.2.2 For severe infections due to XDR-NFGNB strains with borderline susceptibility to the available treatment options, optimized administration of combination therapy using two or more agents should be considered, based on the best options specified in the antibiogram (B-II).

2.2.3 For XDR or PDR *P. aeruginosa* infections, use of ceftolozane-tazobactam may be considered (C-II) or ceftazidime-avibactam (C-I), although there is as yet limited experience of their use in this setting.

2.2.4 If these options are not available or the infection is caused by pan-resistant isolates, it will be necessary to develop combination therapy regimens using two or more agents, choosing those with intermediate susceptibility, or whose MICs are closest to the susceptibility cut-off (C-III).

2.2.5 It is particularly important in these infections to ensure control of the source of infection and to administer high-dose antibiotics with optimized administration regimens, monitoring plasma levels whenever possible (B-II).

Summary of evidence

In general, combination therapy has not been shown to improve the prognosis for *P. aeruginosa* infections, not even in patients with neutropenia.[258] Publications referring to *A baumannii* have had the most varied results on this point, with colistin monotherapy being the most frequently evaluated treatment.[259] It is possible that the variability in results is due, in large measure, to the suboptimal results described for the traditional dosing regimens, which have been shown to be inadequate, especially for treating patients infected by strains with an

increased colistin MIC.[260–262.] Even so, the most recent meta-analysis, which pools the largest number of studies available, has not shown any benefits in terms of clinical response or survival rates for any combination regimen compared with colistin, sulbactam, tigecycline and others in monotherapy,[259] so that there is no evidence to support the systematic use of combination therapy for these infections and it should not be used on a routine basis. Monotherapy with aminoglycosides[236] or tigecycline,[234] on the other hand, is expressly advised against for severe infections.

It should be noted that the possibilities of therapeutic failure could be greater in patients with complicated infections treated with antibiotics showing borderline MICs (susceptible, but bordering resistance),[209,262,263] because it is more difficult in such cases to achieve the PK/PD targets. Hence, in the specific setting of severe infections caused by XDR-NFB where it is necessary to opt for agents with suboptimal activity, combination treatment with more than one agent with *in vitro* activity should be considered. For XDR *P. aeruginosa* infections, combinations of antipseudomonal beta-lactams, colistin, fluoroquinolones, aminoglycosides, fosfomycin and rifampicin have been used; for XDR *A. baumannii* infections, combinations of colistin, carbapenems, sulbactam, aminoglycosides, minocycline and tigecycline have been used. As a general rule, priority should be given to high-dose beta-lactams, if available, administered in extended infusion, because of their better efficacy and safety profiles. [234,264.214]

Ceftolozane-tazobactam and ceftazidime-avibactam have shown variable *in vitro* activity against XDR and PDR *P. aeruginosa* isolates,[265,266] but are not active against *A. baumannii*. Evidence of their effectiveness in this setting is as yet limited. Small series of XDR *P. aeruginosa* infections treated with ceftolozane-tazobactam have been published, reporting success rates close to 70%,[267,268,] which are higher than those that have been traditionally observed,[254,268] although some authors have warned that the incidence of resistance during treatment was considerable.[267] One randomized trial compared ceftazidime-avibactam with the best therapy

available (97% of controls received meropenem) in infections due to ceftazidime-resistant *P. aeruginosa* and demonstrated identical cure rates of 91% in both groups.[269] Although these results are promising, the major limitation of the study was the fact that 94% of infections were urinary tract infections, which limits the reproducibility of the results in more adverse clinical settings. In view of the limited evidence, the use of these agents as first-line therapy in XDR *P. aeruginosa* infections should be limited to cases without other alternative first-line therapeutic options, such as beta-lactams, and the options are restricted basically to colistin and aminoglycosides.

3. –Targeted treatment of Stenotrophomonas maltophilia infections.

Search terms: "*Stenotrophomonas* and treatment".

Recommendations:

3.1 The treatment of choice for infections due to *S. maltophilia* is co-trimoxazole (trimethoprim 15 mg/kg/day in 3-4 divided doses) (C-II).

3.2 In patients with infections with co-trimoxazole-resistant strains, or those who cannot take co-trimoxazole (because of hypersensitivity, for example), the recommended treatment is minocycline (C-II) or fluoroquinolones (C-II) if they are active. There is more limited experience of the use of ceftazidime, tigecycline and colistin in monotherapy (C-III). In the case of patients with serious or refractory infections who require second-line therapy, consider combining two drugs with in vitro activity categorized as susceptible.

Summary of evidence

S. maltophilia is intrinsically resistant to many beta-lactams, including carbapenems, to which can be added an increased incidence of acquired resistance to other antibiotic groups.[270] The recommendations for treating these infections are based on very small observational series.

Co-trimoxazole has the greatest level of activity against *S. maltophilia* isolates (above 90%) and is considered the treatment of choice; it is also the treatment for which there is most clinical experience. [271,272.] Although myelotoxicity secondary to use of co-trimoxazole may be a cause for concern in neutropenic patients, the limited experience available of other treatment regimens and the very high mortality attributable to these infections, leads us to retain co-trimoxazole as the first-line treatment for invasive *S. maltophilia* infections.

For the rest of the antibiotics, there is not even consensus among the different antibiogram committees (CLSI and EUCAST) about which agents to evaluate *in vitro*, because so few studies have correlated *in vitro* activity with clinical results. [229,273.] Three observational studies of limited sample size showed comparable results for patients treated with co-trimoxazole in monotherapy versus minocycline[274] or fluoroquinolones. [275,276.] Tigecycline, ceftazidime and colistin have also been used for treatment of these infections. Cefepime is used much less frequently.[277] Because there is less clinical experience of these second-line drugs, and also because of the possible development of resistance,[271] a combination of two agents with *in vitro* activity can be considered in patients with more severe or refractory infections. This recommendation is based on experimental studies, [271,272] since no clinical study has properly evaluated the benefits of combined treatment.[278]

Table 6. Recommended dosages for the drugs most commonly used in the treatment of infections caused by resistant gram-negative bacilli.

Antibiotic	*Standard dose (i.v.)*	*Recommended dose for serious infections with borderline susceptibility*[d]	*Evidence*
Amoxicillin-clavulanic acid	1.2g/8h	1.2g/6h or 2.2g/8h	BIII
Ciprofloxacin	400mg/12h[a] or 400mg/8h[b]	400mg/8h	CIII
Levofloxacin	500mg/24h[a] or 500mg/12h[b]	500mg/12h	CIII
Ceftazidime	1g/8h[a] or 2g/8h[b]	2g/8h e.i.	CIII
Cefepime	1g/8h[a] or 2g/8h[b]	2g/8h e.i.	BIII
Piperacillin-tazobactam	4.5/8h e.i.	4.5/8h e.i, or 4.5/6h e.i. in critically ill patients	AI
Ceftazidime-avibactam	2/0.5 g/8h		AI
Ceftolozane-tazobactam	1/0.5 g/8h		CIII
Amikacin	15 mg/kg/24h[c]	20 mg/kg/24h[c]	CIII
Gentamicin, tobramycin	5mg/kg/24h[c]	7 mg/kg/24h[c]	CIII
Ertapenem	1g/24h	-	CIII
Meropenem	1g/8h	2g/8h e.i.	BII
Imipenem	0.5g/6h[a] or 1g/6h[b]	1g/6h	CIII
Colistin	3 MU/8h or 4.5 MU/12h	In critically ill patients: LD of 6-9MU	BIII
Tigecycline	LD 100 mg MD 50mg/12h	LD 200mg MD 100mg/12h	BIII
Sulbactam	1g/6h	2g/6h	
Fosfomycin	6g/6h or 8g/8h	-	CIII

Adapted from the Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology, Diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant Enterobacteriaceae.[198]

Indicated doses are for patients with normal renal function.

Abbreviations. LD: loading dose; MD: maintenance dose; e.i.: extended infusion; i.v.: intravenous.

[a]recommended dose for infections caused by Enterobacteriaceae; [b]recommended dose for non-fermenting gram-negative bacteria (NF-GNB); [c]peak and trough levels should be monitored for dose adjustment; [d]dose for patients with normal renal function. Monitor closely for toxicity.

ADJUVANT MEASURES AND PREVENTION

1.- Is the use of colony-stimulating factors indicated for treatment of FN? When?

Search terms: "febrile neutropenia", "colony-stimulating factor", "treatment".

Recommendations:

1. Colony-stimulating factors (CSF) are not routinely recommended for the treatment of FN (B-II).
2. They can be considered for therapeutic use in patients with increased-risk for infection-related complications or predictive factors of poor prognosis (B-II).

Summary of the evidence

Whereas various studies and meta-analyses have shown shorter duration of neutropenia, faster recovery from fever and shorter hospital stays using CSFs, their clinical benefits remain unclear,[279–284] since none has succeeded in demonstrating increased survival.[42] Nonetheless, the guidelines issued by the ASCO (*American Society of Clinical Oncology*),[285] NCCN (*National Comprehensive Cancer Network*)[2] and the AGIHO/DGHO (*Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology*)[163] all recommend considering granulocyte colony-stimulating factors (G-CSF) for therapeutic use if any of the following risk factors are present: age ≥ 65 years, severe neutropenia (ANC < 100/mm^3) or expected to be of long duration (>10 days), sepsis, pneumonia, invasive fungal infection or other clinically documented infection, hospitalization at the time of fever, or previous episode of FN.

2.- When would granulocyte transfusion be indicated?

Search terms: "febrile neutropenia", "granulocyte transfusion".

Recommendations:

1. There is insufficient evidence of the efficacy of granulocyte transfusion in patients with FN and documented infection (C-III).
2. Granulocyte transfusions should be administered only in the context of prospective clinical trials (B-III).

Summary of the evidence

Granulocyte transfusions have been shown to increase the leukocyte count in patients with neutropenia,[286–289] although controlled clinical trials have not demonstrated any clinical benefit or reduction in mortality.[290,291] The heterogeneous nature of the patient populations, types of infection, antimicrobial treatments administered, variable doses of granulocytes transfused, along with the absence of randomization or analyses of parameters of clinical benefit in most of the studies, make it impossible to establish recommendations for use. It continues to be necessary to determine the potential clinical benefit of granulocyte transfusion, which patient populations would benefit from it, and also to specify the indications and therapeutic doses.[292]

3.- Is antibacterial prophylaxis indicated? Which drugs?

Search terms: "febrile neutropenia", "antibacterial prophylaxis".

Recommendations:

1. Antibacterial prophylaxis is not recommended in low-risk patients (A-I).
2. In high-risk patients (ANC <500/mm^3 > 7 days), use of antibacterial prophylaxis should be evaluated on an individual basis in accordance with the characteristics of the patient and local hospital epidemiology, owing to the lack of benefit for mortality and the

increasing levels of resistance in gram-negative bacteria (B-I). If prophylaxis is used, epidemiological surveillance for MDRO detection should be implemented.

Summary of evidence

The efficacy of antibacterial prophylaxis has been studied in a multitude of clinical trials and various meta-analyses. The administration of non-absorbable antibiotics to achieve selective decontamination of the digestive tract, used in the first studies in the 1970s, was abandoned due to the lack of systemic activity, tolerability and the emergence of resistant microorganisms.[293] Later trials using co-trimoxazole showed no differences in mortality,[294] above all, because it did not cover *P. aeruginosa* and it also increased myelotoxicity. A wide variety of later studies demonstrated the usefulness of quinolones for this indication.[295,296] Nevertheless, the potential epidemiological impact, with an increase in infections caused principally by resistant gram-negative bacteria,[297–299] or Gram-positives such as the viridans streptococci[300] and associated toxicities (QT interval prolongation, tendinopathy) led many centers to suspend routine use of antibacterial prophylaxis.

In high-risk patients (ANC<500/mm^3 for > 7 days), [42] most clinical trials were performed with fluoroquinolones, generally ciprofloxacin or levofloxacin, because of their broad-spectrum antibacterial activity, safety profile and oral bioavailability. In an early meta-analysis, antibiotic prophylaxis with fluoroquinolones was beneficial in terms of reducing mortality, episodes of fever and bacterial infections in high-risk patients.[301,302] In a more recent meta-analysis[303] that included 109 randomized studies, prophylaxis reduced all-cause mortality versus placebo or non-intervention, as well as infection-related mortality, incidence of fever and clinically documented infections. The estimated number of patients that need to be treated to prevent one febrile episode is 5, while six are needed to prevent one microbiologically documented infection, and 43 to prevent a death.

The most recent meta-analysis[119] includes all studies between 2005-2014 (2 randomized and 12 observational) and demonstrates that use of fluoroquinolones has no effect on mortality, but is associated with a lower incidence of bloodstream infections and fever episodes during neutropenia. Some studies have reported an increase in colonization or infection due to multidrug-resistant or quinolone-resistant bacteria. In conclusion, the authors advise weighing up their benefits on the one hand, against their toxicities and local epidemiological impact on the other, before using them.

Clinical trials combining a fluoroquinolone and an antibiotic with anti-Gram-positive activity also showed reductions in the number of episodes of FN and of infections due to *Staphylococcus* spp. and *Streptococcus* spp., without achieving reductions in infection-related mortality.[304] At the same time, an increase in breakthrough bacteremia caused by resistant Gram-positive and gram-negative pathogens was reported. [22,298,299]

A more recent study compared levofloxacin with a third-generation cephalosporin in high-risk patients[305] and found no differences in the number of episodes of febrile neutropenia or time-to-positivity of cultures, with an increase in *Enterobacter* spp. in those who received cephalosporins.

In intermediate-risk patients with neutropenia of 7–10 days duration (autologous HSCT, lymphoma, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), purine analogues),[2,306,307] the benefit of prophylaxis is less than in high-risk patients, and offers no advantage for survival. The indication of prophylaxis in intermediate-risk patients should take other factors into account, such as the age of the patient, previous episodes of FN, advanced disease, etc.[14]

Antibacterial prophylaxis is not universally recommended for low-risk patients.[2,42,308,30] As with intermediate-risk patients, it may be considered in specific situations and tailored to the individual. Although randomized trials have demonstrated that prophylaxis has a certain

protective effect[306] since it reduces the episodes of FN and avoids hospital admission, especially in the first cycle of chemotherapy,[310] the estimated number of patients who need to be treated in order to prevent one infection is very high (around 250).[311] Taking into account the economic cost, adverse effects, selection of resistant bacteria and infections such as *C. difficile*,[298,312–314] prophylaxis is not routinely indicated for low-risk patients.

The potential bacterial resistance to quinolones gives cause for concern. The emergence of resistance is determined by the overall use of the drug in the community, and its efficacy is reduced when the resistance rate in gram-negative bacteria exceeds 20%.[308,313,315,316] One Spanish study[314] demonstrated the emergence of quinolone-resistant *E. coli* in 35% of stool samples taken from patients receiving prophylaxis within a median of 10 days (range: 3–35 days) of starting antibiotics, which indicates that changes in susceptibility occur within a short space of time, as other studies have confirmed.[317–319]

In a recent multicenter study,[16] 50% of bacteremias caused by gram-negative bacteria in the first six months after transplantation were due to quinolone-resistant organisms and non-carbapenem antibiotics. When centers that gave quinolone prophylaxis were compared with those that did not, the rate of resistance to quinolones rose to 79%, resistance to non-carbapenem antibiotics was 36%, as against 13%, which calls into question prophylaxis in this setting. The use of fluoroquinolones moreover has also been related to the emergence of MRSA, colonization with *C. difficile* and vancomycin-resistant enterococci.[320]

The current recommendations of the majority of guidelines agree that antibacterial fluoroquinolone prophylaxis would only be indicated in patients undergoing allogeneic-HSCT and receiving induction therapy for acute leukemias.[2,42.] Nevertheless, the recommendation is open to challenge, since the early meta-analyses that endorsed it did not use an appropriate methodology. Furthermore, the various studies were carried out at a time when the bacterial epidemiology was completely different from the one today. Table 7 shows the recommendations

of the various therapeutic guidelines.[2,42,159,308–310] The most restrictive with respect to prophylaxis are the Australian guidelines,[308] which are dictated by the increase in resistant microorganisms.

If it is decided to use antibacterial prophylaxis,[1,159,308–310] the options are: levofloxacin (500 mg/day), ciprofloxacin (500 mg/12 hours), ofloxacin (200-400 mg/12 hours) or norfloxacin (400 mg/12 hours). In patients at increased risk of mucositis due to the higher incidence of viridans group streptococcal infection, levofloxacin would be indicated in preference to ciprofloxacin.[1] In general, it is not advised to combine fluoroquinolones with antibiotics against Gram-positive organisms.[1]

Factors to be assessed before starting:

- Factors to do with the patient: risk of prolongation of the QT interval, especially in patients receiving other drugs with the same effect (azoles, metronidazole, macrolides)
- Epidemiological factors associated with the center or local epidemiology:
    - increased risk of resistance development in gram-negative, and also Gram-positive microorganisms.
    - greater incidence of *C. difficile* infections, although this has not been proven in neutropenic patients.
    - reduced efficacy if there are high rates of fluoroquinolone resistance in the geographical region.

The duration of prophylaxis has not been sufficiently studied. It is normally started on the first day of cytotoxic chemotherapy, or after its completion, and is discontinued when the neutropenia resolves or when empirical antibiotic therapy for FN is started.[1,308,310]

As a general rule, it is recommended that all centers where fluoroquinolone prophylaxis is administered should implement monitoring for the emergence of resistance.[1,308–310] In addition,

prophylaxis should be adapted to the treatment regimen and not be administered as first-line treatment in an outpatient setting if fever appears.

The most recent meta-analysis concluded that the effect of prophylaxis on overall mortality had not been demonstrated and its authors advised weighing up the potential benefits of prophylactic use against its impact on toxicity and local epidemiology before deciding whether to implement it.[119] Furthermore, a multicenter study by the EBMT group[16] reported a high rate of resistance to quinolones and non-carbapenem antibiotics in patients who received prophylaxis with quinolones, which raises the question of whether or not it is necessary to administer them universally, even in high-risk patients.

The present antibiotic policy is tending towards less universal use of antibiotics and especially reducing the duration of antibiotic treatment. Hence, use of antibacterial prophylaxis should be assessed on an individual basis, taking into account the characteristics of the patient and the epidemiology of the center where he/she is treated. If it is decided to implement prophylaxis, it is recommended to maintain vigilance in order to detect the emergence of MDROs. In low-risk patients, our position is unquestionably against its use.

3 – Is prophylaxis with colony stimulating factors indicated? When?

Search terms: "febrile neutropenia", "colony stimulating factor", "prophylaxis"

Recommendations:

1. The decision to use colony-stimulating factor prophylaxis for the prevention of FN should be based on the relative myelotoxicity of the chemotherapy regimen and the presence of potential risk factors, which should be evaluated before each cycle of chemotherapy is administered.
2. In situations where chemotherapy dose intensity or dose density strategies confer a survival benefit, prophylaxis with G-CSF should be used as supportive treatment (A-I).

3. Primary prophylaxis is recommended from the first chemotherapy cycle for patients whose overall risk of FN is ≥ 20%, based on patient-related, disease-related and regimen-related risk factors (A-I).
4. When the overall risk of FN is 10%–20%, attention should be focused on additional risk factors (such as comorbidities or advanced age), which increase the risk of FN and support an indication of prophylaxis with G-CSF (A-I).
5. Prophylaxis with G-CSF is not recommended if chemotherapy has an FN risk of <10% (A-I).
6. Secondary prophylaxis is recommended for patients who experienced neutropenic complications in a previous cycle of chemotherapy and in whom a dose reduction or delay in treatment could compromise progression-free or overall survival, or treatment outcome (A-I).
7. Prophylaxis can be given with any of the following factors (filgrastim, lenograstim and pegfilgrastim) or any of their available biosimilars (A-I), preferably subcutaneously.

Summary of the evidence

A systematic review and meta-analysis of 17 randomized clinical trials of primary prophylaxis with granulocyte colony-stimulating factors (G-CSF), which included some 3,500 patients with solid tumors or lymphomas, confirmed a significantly reduced risk of FN in each one of the trials.[321] Another more recent systematic review of 59 randomized clinical trials concluded that primary prophylaxis with G-CSFs reduces mortality in patients with neoplasia. The largest reductions in all-cause mortality were found in patients with lymphoma and lung cancer. A reduction in mortality was also found when trials including older patients were analyzed.[322] The guidelines based on the evidence of the *European Organization for Research and Treatment of Cancer* (EORTC)[323] recommend basing the decision on the relative myelotoxicity of the

chemotherapy regimen[324] and potential risk factors, which should be evaluated before each cycle of chemotherapy. Particular consideration should be given to the increased risk in older patients (age ≥ 65 years). Other adverse factors that may influence the risk of FN are: advanced stage of disease, previous episodes of FN and absence of prophylactic antibiotics.

In situations when chemotherapy dose intensity or dose density confer a survival benefit, as is the case in patients with high-risk breast cancer or receiving intensive chemotherapy for urothelial carcinoma, prophylaxis with G-CSF should be used as supportive treatment. There is limited information however for non-Hodgkin lymphoma. In practice, many chemotherapy protocols have incorporated use of G-CSF into their treatment regimen.

The updated *American Society of Clinical Oncology* (ASCO) guidelines[285] recommend primary prophylaxis from the first cycle of chemotherapy in patients whose risk of FN is ≥ 20%, based on risk factors associated with the patient, the disease and the treatment. It should be highlighted that the risk of an initial episode of FN is greatest during the first cycle of treatment when the patient is generally receiving full dose intensity.[325,326] Specifically, prophylaxis with G-CSF should be considered for patients aged ≥ 65 years with aggressive lymphoma being treated with immunochemotherapy with curative intent (R-CHOP), particularly if there are comorbidities (B-II).

Likewise, they recommend secondary prophylaxis in patients who experienced neutropenic complications in a previous cycle of chemotherapy, and whose progression-free survival, overall survival or treatment outcome could be compromised by dose reduction or delay in treatment.

Finally, the guidelines of the *National Comprehensive Cancer Network* (NCCN)[2] recommend that the decision be based on the relative myelotoxicity of the chemotherapy regimen and on an assessment of potential risk factors before each chemotherapy cycle. The risk assessment includes the underlying disease, chemotherapy regimen (high-dose, dose-dense or

standard dose, patient risk factors and intention-to-treat (curative/adjuvant or palliative)). Based on the chemotherapy regimen and the patient-related risk factors, the risk of FN is considered to be high (≥20%), intermediate (10%-20%) or low (<10%). The main risk factors for FN based on a systematic review of the literature[327] are:

1. Previous chemotherapy or radiation therapy

2. Prolonged neutropenia

3. Metastatic bone marrow infiltration

4. Recent surgery and/or open wounds

5. Hepatic dysfunction (bilirubin >2 mg/dL)

6. Renal dysfunction (creatinine clearance <50 mL/min)

7. Age >65 years and full-dose chemotherapy

In summary, routine use of G-CSF is indicated from the first cycle of myelosuppressive chemotherapy (primary prophylaxis) when the overall risk of FN is ≥ 20%. When the risk is 10%–20%, particular attention should be paid to additional risk factors, such as comorbidities or advanced age, which can increase the risk of FN and support the indication of prophylaxis with G-CSF. Prophylaxis with G-CSF is not recommended if the risk of FN associated with chemotherapy is <10%.

Another important aspect is which type of G-CSF should be employed.[328] Any of the following factors (filgrastim, lenograstim and pegfilgrastim), as well as any biosimilars available may be used, preferably given subcutaneously. Filgrastim is a non-pegylated form of G-CSF used at a daily dose of 5 μg/kg, starting 24–96 hours after completing chemotherapy. Pegfilgrastim is a long-acting, pegylated form of G-CSF that requires less frequent administration than the non-pegylated form, a single dose of 6 mg once per chemotherapy cycle, administered 24–72 hours after completing chemotherapy. If pegfilgrastim has been given, filgrastim cannot be given in the

event of FN. The choice of agent depends on convenience, cost and clinical situation. In everyday practice, the various G-CSFs are used for the prevention of neutropenia and FN. Different clinical practice guidelines or recommendations have not opted for any factor in particular on the basis of efficacy or safety, apart from considerations associated with greater comfort for the patient and convenience associated with the chemotherapy regimen.

Table 7.- Indications and recommendations for febrile neutropenia prophylaxis according to different therapeutic guidelines: Allo-HSCT: allogeneic hematopoietic stem cell transplantation; auto-HSCT: autologous hematopoietic stem cell transplantation; GVHD: graft-versus-host graft disease; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia

GUIDELINES	INDICATIONS	PATIENTS	CONSIDERATIONS	ANTIBIOTIC/EVIDENCE
IDSA [42]	ANC<100/mm^3 and >7 days (BI)		Do not combine quinolones with antibiotics against Gram-positive organisms and (A-I) Monitor the emergence of resistance (A-II) No routine prophylaxis for neutropenia <7 days (A-I)	Ciprofloxacin 500 mg/12h or levofloxacin 500 mg/24h (AI)
NCCN 2016 [329]	High-risk	Allo-HSCT AML in induction and consolidation treatment with alemtuzumab		Fluoroquinolones
	Intermediate risk	GVHD with steroids Neutropenia >10 days Auto-HSCT Lymphoma Multiple myeloma, Purine analogues CLL Neutropenia >7 days		
German guidelines (AGIHO) [310]	High-risk (AI) Duration of neutropenia >7 days or with additional risk factors (type of base disease, age, comorbidities, immunosuppressants)		Low-risk (neutropenia <7 days) in first cycle of chemotherapy, the elderly, history of previous infections	Ciprofloxacin 500 mg/12h or levofloxacin 500 mg/24h (A-I)
ECIL guidelines 2005[159]	High-risk (Neutropenia >7 days)	Allo-HSCT AML in induction Auto-HSCT		Levofloxacin (500 mg/24h) (A-I), ciprofloxacin (500/12h) (A-I), ofloxacin (200-400 mg/12h) (B-I), norfloxacin 400 mg/12h (B-I)
British guidelines (NICE) [309]	ANC<500/mm^3 and >7 days	Acute leukemias Allo-HSCT Auto-HSCT		Fluoroquinolones during neutropenia
Australian guidelines[308]	Not routinely used in high-risk (category C)	Considered in HSCT, home treatment, and patients with bone marrow failure in palliative treatment (category C)	Epidemiological surveillance if quinolones are used (category C) Not effective if resistance rate is >20%	Fluoroquinolones

Conflicts of interest

Carlota Gudiol has served as speaker at scientific meetings sponsored by Pfizer, MSD, Astellas and Gilead. Rafael de la Cámara has participated as speaker at scientific meetings sponsored by MSD, GSK, Novartis, Astellas, Pfizer and Gilead; and in consultancy and advisory activities for Novartis, MSD, Janssen, Clinigen and Astellas. Manuel Lizasoain has participated as speaker at scientific meetings sponsored by Pfizer, MSD and Gilead. Jordi Carratalà has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead and Angelini. Rafael Cantón has participated as speaker at scientific meetings sponsored by Angelini, ERN Laboratorios, MSD, Pfizer and Zambon and has received funding for research projects from AstraZeneca and MSD. Manuela Aguilar-Guisado has participated as speaker at scientific meetings sponsored by Pfizer and MSD. Manuela Aguilar-Guisado has participated as speaker at scientific meetings sponsored by Pfizer and MSD. José Molina Gil-Bermejo has received lecturing fees in activities financed by Merck Sharp & Dohme, and has received grants to attend conferences organized by Astellas Pharma. Carlos Solano has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Astellas and Gilead He has received grants for clinical and preclinical research from Pfizer and Astellas. Carolina García-Vidal has received fees for speaking at events sponsored by Gilead Science, Merck Sharp and Dohme, Pfizer, Janssen and Novartis, and has received a subsidy from Gilead Science. María Lourdes Vázquez López has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead, Astellas, Amgen. José Ramón Azanza has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead, Janssen, AstraZeneca, Roche. José Ramón Azanza has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead, Janssen, AstraZeneca, Roche Francisco Javier Candel has participated as speaker scientific meetings sponsored by Pfizer, MSD, Gilead, Angelini, Astellas, and ERN. Isabel Ruiz-Camps has participated as speaker at scientific meetings sponsored by

Astellas, Celgene, Gilead, MSD, Pfizer and in scientific consultancy for Astellas, Gilead, and Pfizer. María Suárez-Lledó has participated as speaker at scientific meetings and has collaborated in scientific studies sponsored by Pfizer and MSD. Isidro Jarque has participated as speaker at scientific meetings sponsored by Gilead, MSD, and Pfizer. Isabel Sánchez-Ortega has no conflicts of interest.

Acknowledgements

The authors would like to thank Antonio Gutiérrez-Pizarraya for his comments and technical support in the preparation of this document. They would also like to thank the members María Illescas and Juan Manuel García-Lechuz Moya for their comments from society members during the revision phase of the document.

8. Appendices:

Table 8: Dosage regimens and hepatic and renal impairment [330–340]

	Cr Cl ml/min				CHILD-PUGH		
	> 50	50-30	30-10	< 10	A	B	C
Penicillin G	1-3 MU/4-6 h	NC	1-3 MU/8 h	1-2 MU/12 h	NC	NC	NC
Cloxacillin	1-2 g/4-6 h	NC	0.5-1 g/12-24h	0.5-1 g/12-24 h	NC	NC	NC
Ampicillin	0.5-2 g/6-8 h	NC	1-2 g/8 h	1 g/12 h	NC	NC	NC
Amoxicillin	1-2 g/8 h	NC	0.5 g/12 h	0.5-1 g/24 h	NC	NC	NC
Amoxicillin/clavulanic	1-2 g/6-8 h	NC	0,5 g/12 h	0,5-1 g/24 h	NC	NC	NC
Piperacillin/ tazobactam	2-4 g/4-6 h	NC	4 g/8 h	4 g/12 h	NC	NC	NC
Cefazolin	1-2 g/8 h	NC	0.5-1 g/8 h	0.5-1 g/24 h	NC	NC	NC
Cefepime	1-2 g/8-12 h	1-2 g/12 h	1 g/12 h	1 g/24 h	NC	NC	NC
Cefuroxime	0.75-1.5 g/8 h	NC	0.75-1.5 g/12 h	0.75 g/24 h	NC	NC	NC
Cefotaxime	1-2 g/4-8 h	NC	NC	2 g/24 h	NC	NC	NC
Ceftaroline	0.6 g /8-12 h	0.4 g/8-12 h	0.3 g/8-12 h	0.2 g/12 h	NC	NC	NC
Ceftazidime	1-2 g/8-12 h	1-2 g/12 h	1 g/24 h	1 g/24-48 h	NC	NC	NC
Ceftazidime/Avibactam	2.5 g/8 h	1-2 g/12 h	1 g/24 h	1 g/24-48 h	NC	NC	NC
Ceftolozane/Tazobactam	1.5-3 g/8 h	0.75 g/8 h	0.375 h/8 h	Initial dose 0.75 g, followed by 0.15 g /8 h	NC	NC	NC
Ceftriaxone	1-2 g/12-24 h	NC	NC	1-2 g/24 h	NC	NC	NC
Aztreonam	1-2 g/8-12 h	NC	NC	Initial dose 1-2 g, followed by 0.5 g/8-12 h	NC	NC	NC
Imipenem	0.5-1 g/6-8 h	0.5 g/6 h	0.5 g/8 h	0.5 g/12 h	NC	NC	NC
Meropenem	0.5-1 g/6-8 h	1 g/8 h	1 g/12 h	1 g/24 h	NC	NC	NC
Ertapenem	1 g/12-24 h	NC	0.5 g/24 h	0.5 g/24 h	NC	NC	NC
Amikacin	15 mg/kg/24 h	12 mg/kg/24 h	12 mg/kg/48 h	7.5-10 mg/kg/48 h	NC	NC	NC
Gentamicin	5-7 mg/kg/24 h	5 mg/kg/24 h	5 mg/kg/48 h	3 mg/kg/24-48 h	NC	NC	NC
Tobramycin	5-7 mg/kg/24 h	5 mg/kg/24 h	5 mg/kg/48 h	3 mg/kg/24-48 h	NC	NC	NC
Colistin	Initial dose 6-9 MU, followed by 2-3 MU/8 h or 4.5 MU /12 h	6 MU/ 24 h	4.5-5.5 MU/ 24 h	3 MU/ 24 h	NC	NC	NC
Tigecycline	Initial dose 0.1 g followed by 0.05 g/12 h	NC	NC	NC	NC	NC	25 mg/12 h
Clarithromycin	0.5 g/8-12 h	NC	0.6 g/24 h	0.5 g/24 h	0.25 g/8-12 h	0.25 g/8-12 h	0.25 g/8-12 h
Azithromycin	0.5 g/24 h	NC	NC	NC	NC	NC	NC
Clindamycin	0.6-0.9 g/8 h	NC	NC	NC	NC	NC	NC
Metronidazole	Initial dose 15 mg/kg, followed by 0.5 g/8 h	NC	NC	0.5 g /12 h	NC	0.25 g/8 h	0.25 g/8 h
Vancomycin	15-20 mg/kg/12 h	NC	1 g/48 h	1 g/5-10 d	NC	NC	NC
Teicoplanin	6 mg/kg/24 h	6 mg/kg/48 h	6 mg/kg/72 h	6 mg/kg/72 h	NC	NC	NC
Dalbavancin	Initial dose 1 g, and 0.5 g after 7 days or 1.5 g SD	NC	0.75 g SD 0.375 after 7 days	0.75 g SD 0.375 after 7 days	NC	NC	NC
Daptomycin	6-10 mg/kg/24h	NC	6-8 mg/kg/48 h	4-6 mg/kg/48 h	NC	NC	Caution
Linezolid	0.6 g/12 h	NC	NC	NC	NC	NC	NC
Tedizolid	0.2 g/ 24 h	NC	NC	NC	NC	NC	NC

Fosfomycin sodium	0.1-0.3 g/kg/day in 3-4 doses	4 g/12 h	4 g/24 h	2 g/24 h	NC	NC	NC
Levofloxacin	0.5 g/12- 24 h	NC	0.5 g/24 h	0.25-0.5 g/48 h	NC	NC	NC
Ciprofloxacin	0.4 g/8-12 h	NC	0.2 g/8-12 h	0.4 g/24 h	NC	NC	NC
Moxifloxacin	0.4 g/24 h	NC	NC	NC	NC	NC	NI
Trimethoprim-sulfamethoxazole	0.16/0.8 g/8-12 h	NC	0.16/0.8 g/24 h	0.08/0.4 g/24 h	NC	0.08/0.4 g/12 h	Avoid
Liposomal amphotericin B	1-3 mg/kg/24 h	NC	NC	NC	NC	NC	NC
Amphotericin B lipid complex	5 mg/kg/24 h	NC	NC	NC	NC	NC	NC
Itraconazole	0.2 g/12 h for 2-3 days, then 0.2 g/ 24 h	NC	NC	Avoid (iv)	NC	NC (2)	NC (2)
Fluconazole	Initial dose 12 mg/kg, followed by 6 mg/kg/24 h	3 mg/kg/24 h	3 mg/kg/24 h	3 mg/kg/24 h	NC	NC (2)	NC (2)
Voriconazole	Initial dose 6 mg/kg/12 h, followed by 4 mg/kg/12 h	With caution via the intravenous route to avoid accumulation of excipients	With caution via the intravenous route to avoid accumulation of excipients	With caution via the intravenous route to avoid accumulation of excipients	NC	2 mg/kg/12 h	Avoid
Posaconazole	Initial dose 300 mg/12 h, then 0.3 g 24 h	NC	NC	NC	NC	Caution	Caution
Isavuconazole	0.2 g/8 h, for 48 h, then 0.2 g/24 h	NC	NC	NC	NC	NC	Caution
Caspofungin	Initial dose 70 mg, then 50 mg/24 h	NC	NC	NC	NC	0.035 g/24 h	Avoid
Micafungin	0.1-0.15 g/ 24 h	NC	NC	NC	NC	NC	Avoid
Anidulafungin	Initial dose 0.2 g, then 0.1 g/ 24 h	NC	NC	NC	NC	NC	NC
Acyclovir	5 mg/kg/12 h	NC	NC	2.5 mg/kg/24 h	NC	NC	NC
Ganciclovir	5 mg/kg/12 h	2.5 mg/kg/12 h	2.5 mg/kg/24 h	1.25 mg/kg/24 h	NC	NC	NC
Valganciclovir	0.9 g/12 h	0.9 g/12 h	0.9 g/24 h	0.5 g three days a week	NC	NC	NC
Foscarnet	90 mg/kg/12 h for 2 weeks, then 120 mg/kg/24 h	60 mg/kg/12 h	60 mg/kg/24 h	Avoid	NC	NC	NC

SD: single dose. NC: no change. NI: no information

Table 9. Dosage using hemodialysis filtration techniques[341–346]

	MW (Da)	FP (%)	VD (l/kg)	HD	HD Supplement	CVVHD
Penicillin G	334	50	0.15	2 MU/12 h	PD dose	3 MU/4-6 h
Cloxacillin	435	91	0.15	1 g/12-24 h	PD dose	0.5-1 g/12 h
Ampicillin	349	15	0.18	1-2 g/12-24 h	PD dose	1-2 g/12-24 h
Amoxicillin	365	17	0.18	2 g/24 h	PD dose	1-1.5 g/12 h
Clavulanic acid	199	25	0.2	1 g/24 h	PD dose	0.5 g/12 h
Piperacillin	539	21	0.2	3-4 g/12 h	PD dose	2 g/6-8 h
Tazobactam	300	23	0.2	3-4 g/12 h	PD dose	2 g/-8 h
Cefazolin	454	80	0.13	0.5-1 g/24 h	0.5 g	1g/8 h or 2 g/12 h
Cefepime	480	17	0.22	0.5-1 g/24 h	0.5-1 g	1g/8 h or 2 g/12 h
Cefuroxime	424	40	0.2	0.75 g/24 h	PD dose	0.75 g/24 h
Cefoxitin	427	70	0.13	0.5-1 g/24 h	1 g	2 g/24 h
Cefotaxime	455	40	0.25	1-2 g/12-24 h	1 g	1-2 g/6-8 h
Ceftaroline	774	20	0.3	0.2g/12 h	PD dose	NI
Ceftriaxone	554	95	0.1	1-2 g/24 h	No	1-2 g/12-24 h
Ceftazidime	546	17	0.2	1 g/24-48 h	1 g	1g/8 h or 2 g/12 h
Ceftolozane	666	20	0.2	0.75 SD, then 0.15 g/8 h	PD dose	NI
Avibactam	265	8	0.2	NI	NI	NI
Aztreonam	435	50	0.2	0.5-1 g/24 h	0.5 g	1g/8 h or 2 g/12 h
Imipenem	317	20	0.2	0.25-0.5 g/12 h	0.25 g	0.5 g /6-8 h
Meropenem	386	2	0.2	0.5 g/24 h	0.5 g	0.5 g -1 g/8-12 h
Ertapenem	475	95	0.15	0.5 g/24 h	0.15 g	0.5 g g/24 h
Amikacin	585	4	0.2	5-7.5 mg/kg/48 h	7.5 mg/kg	9-12 mg/kg/24 h
Gentamicin	477	5	0.2	1.5 mg/kg/48-72 h	1.5-2.5 mg/kg	1.5 mg/kg/24 h
Tobramycin	467	1	0.2	1.5 mg/kg/48-72 h	1.5-2.5mg/kg	1.5 mg/kg/24 h
Colistin	1155	10	0.09	Days without HD: 2.2-2.3 MU/day. Days with HD: 3 MU/day, after HD. Recommended to administer twice daily .	PD dose	2-3 MU/8 h or 4.5 MU /12 h
Tigecycline	585	80	7	50 mg/12 h	No	NC
Fosfomycin	138	0	0.31	2-4 g/24 h	PD dose	NI
Erythromycin	733	75	0.72	1 g/6-8 h	No	1 g/6-8 h
Azithromycin	748	22	2.3	0.25-0.5 g/24 h	No	NC
Clindamycin	424	60	1	0.6-0.9 g/8 h	No	NC
Metronidazole	171	12	0.9	0.5 g/8-12 h	No	0.5 g/6-12 h
Vancomycin	1449	55	0.3	-	5-10 mg/kg PD	7.5-10 mg/kg/12 h
Teicoplanin	1877	90	1.1	6 mg/kg/72 h	No	6 mg/kg/48 h
Dalbavancin	1816	93	0.2	NC	No	NC
Daptomycin	1620	90	0.1	4-6 mg/kg/48 h	PD dose	NC
Linezolid	337	31	0.8	0.6 g/12 h	PD dose	NC
Tedizolid	370	80	1	NC	No	NC
Levofloxacin	361	35	2	0.25-0.5 g/48 h	No	0.25-0.5 g/24-48 h
Ciprofloxacin	331	25	3	0.4 g/24 h	No	0.4 g/12 h
Moxifloxacin	401	40	2	0.4 g/24 h	No	NC
Trimethoprim-	290	44	1.4	2,5-10 mg/kg/24 h	No	2.5-7.5 mg/kg/12 h
Sulfamethoxazole	250	60	0.3			
Liposomal amphotericin B			0.5	3-5 mg/kg/24 h	No	NC
Amphotericin B lipid complex				5 mg/kg/24 h	No	NC
Itraconazole	705	99	9	Avoid iv route; oral route: NC	Avoid iv route; oral route: NC	Avoid iv route; oral route: NC
Fluconazole	306	12	1	0.2-0.4 g/48-72 h	PD dose	0.2-0.4 g/24 h
Voriconazole	349	58	4.6	Avoid iv route; oral route: NC	Avoid iv route; oral route: NC	Avoid iv route; oral route: NC
Posaconazole	700	98	10	0.4 g/12 g	NI	NI
Isavuconazole	437	99	65	NC	No	NI
Caspofungin	1093	99	0.3	0.05 g/24 h	No	NC
Micafungin	1292	99	0.3	0.1 g/24 h	No	NC
Anidulafungin	1140	99	0,4	No changes	No	NI
Acyclovir	225	15	0,7	2.5-5 mg/kg/24 h iv	2.5 mg/kg	5-10 mg/kg/day

Ganciclovir	255	1	0,74	1.25 mg/kg/48-72 h	PD dose	2.5 mg/kg/12 h
Foscarnet	126	15	0,5	Avoid	NI	NI
Ribavirin	244	0	64	0.6-1.2 g/ 12 h	No	NI

MW: molecular weight. FP: fraction of drug bound to protein. VD: Volume of distribution. HD: dosage administration for hemodialysis patients. HD supplement: dose to be administered as a supplement to the prescribed regimen (No: it is not necessary to administer dose after the dialysis session). CVVHD: Continuous venovenous hemodiafiltration. PD Dose: dose should be administered at the end of or as close as possible to the end of the hemodialysis session. NC: no change in dose. NI: no information.

In general, drugs with a high volume of distribution, a high degree of plasma protein binding, and low molecular weight are not dialyzable and cannot be filtered out using external techniques, except in the case of plasmapheresis, which eliminates a large proportion of drugs with high protein binding (>80%).

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