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CLINICAL GUIDES IN ONCOLOGY

Management of infection and febrile neutropenia in patients with solid cancer

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Abstract An expert group from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC, for its acronym in Spanish) and the Spanish Society of Medical Oncology (SEOM, for its acronym in Spanish) have reviewed the main aspects to be considered when evaluating patients with solid cancer and infectious complications contained in this article. Recommendations have, therefore, been put forth regarding the prophylaxis of the most prevalent infections in these patients, the use of vaccines, measures to control infection through vascular catheters, and preventing infection in light of certain surgical maneuvers. The following is a revision of the criteria for febrile neutropenia management and the use of colony-stimulating factors and closes with several guidelines for treating the cancer patient with serious infection. The document concludes with a series of measures to control hospital infection.

Keywords Cancer · Febrile neutropenia · Infection · Prophylaxis · Risk factors

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Introduction

Over the course of the last two decades, substantial headway has been made in the treatment of the cancer patient. Undoubtedly, one of the most outstanding advances has been the decrease in infection-related morbimortality due to the progress achieved in preventing and treating these infections, as well as in shortening the period of neutropenia, thanks to the use of hematopoietic growth factors.

Despite these advances, infectious complications continue to be one of the main causes of death in oncological patients. These individuals are subject to greater risk of certain infections being reactivated and are more likely to suffer nosocomial pathogens as a consequence of surgeries, the use of venous or urinary catheters and other devices, as well as the procedures they undergo. The emergence of multiresistant microorganisms in recent years has complicated the issue of antibiotherapy in this population even further. Moreover, the growing use of new monoclonal antibodies and biological therapies has incremented the possibility of certain serious infections in these patients.

While there are numerous clinical guidelines addressing the hematologic patient, few focus specifically on people with solid tumors. Experts from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC, for its acronym in Spanish) and the Spanish Society of Medical Oncology Médica (SEOM, for its acronym in Spanish) have, therefore, undertaken to elaborate this document, in which the pertinent information currently available has been reviewed and recommendations based on the best evidence available have been put forth, in the hope that they will help oncologists and specialists in infectious medicine in their daily clinical practice and urge them to manage these patients together, in pursuit of optimal care for cancer patients with infectious disease.

Initial evaluation

The initial evaluation of cancer patients undertakes to detect active or latent infections at risk for reactivation in individuals with solid cancer who are to undergo potentially immunosuppressant treatment.

The clinical assessment should include: (1) history of infectious diseases that may have remained latent and reactivate in the event of immunosuppression; (2) full epidemiological history, including contacts with patients with infectious disease, as well as with other immunodepressed individuals; (3) patient's origin and any visits or trips to countries outside our geographical area with endemic diseases that could be revived, and (4) history of possible drug reactions to antimicrobials. In women, a gynecological checkup is also advised, as is screening for the human papilloma virus (HPV).

The initial microbiological assessment is aimed at screening for the most common chronic or latent infections that may recrudesce in the event of immunosuppression and will depend on the type of chemotherapy administered and on the specific risk of immunosuppression in each person. In general, depending on the chemotherapy, duration, immunosuppressant probability, and on the type of patient and their perspectives for survival, it is advisable to know the serology for: (1) hepatitis A, B, and C virus (HAV, HBV, and HCV); (2) varicella zoster virus (VZV), and (3) human immunodeficiency virus (HIV). Likewise, tuberculosis (TBC) must be ruled out in the event of any uncertainty in this regard, people in contact with TBC or at risk populations, such as institutionalized individuals. There are regional diseases that must be taken into consideration in patients from certain geographical areas (Table 1).

Prevention

Vaccination

Table 2 contains the agents (obligatorily inactivated) to be used in these cases [1]. Vaccines containing attenuated live microorganisms such as the rotavirus, 3-in-1 viral vaccine (measles, mumps, rubella), and chicken pox are contraindicated during chemotherapy [2].

Patients with active solid tumors and those undergoing chemotherapy must be vaccinated yearly for the flu [2]. It is recommended that they be immunized against pneumococcus in accordance with the guidelines for immunodepressed patients.

Depending on the aforementioned characteristics (type of chemotherapy, duration, clinical status), a booster dose should be given against tetanus and diphtheria. Those who have not been protected against pertussis should be given the diphtheria, tetanus, and acellular pertussis vaccine (DTaP). Likewise, HPV, meningococus, and HAV inoculations must be administered whenever there is a specific indication. Immunization against HBV must be contemplated in unprotected individuals, after assessing their serological and clinical status.

The previously indicated agents should be given prior to initiating chemotherapy. Inactivated vaccines should be administered at least 2 weeks before beginning treatment (with the exception of the flu vaccine, which will be given yearly, even during chemotherapy), whereas attenuated live vaccines must be administered at least 4 weeks prior to commencing treatment [3].

Table 1 Regional or imported diseases by geographical area of procedence

Country of procedence	Probable microorganism	Screening technique
Mexico, Panama, Venezuela, Guatemala, or Southern US	*Histoplasma capsulatum*	Serology
Southern US, Mexico, Guatemala, Honduras, Nicaragua, Argentina, Paraguay, Venezuela, and Colombia	*Coccidioides immitis*	Serology
Caribbean, Southern Japan, Central and South America, Sub-Saharan Africa	*HTLV-I-II*	Serology
Mexico, Central America, or Southern Cone (Chile, Argentina, Bolivia, Brazil, Paraguay)	*Trypanosoma cruzi*	Two serological techniques
Tropical and subtropical regions, including Southern US	*Strongyloides stercoralis*	Agar technique Feces culture Serology
Endemic areas for malaria during the last 2–5 years: asymptomatic parasitemias should be ruled out	*Plasmodium sp*	PCR Thick blood film

HTLV-I-II: human T cell lymphotropic virus types I and II; PCR: polymerase chain reaction

Table 2 Recommended vaccines for adults with solid tumors

Vaccine	Recommendation	Regimen
Pneumococcus	Recommended	1st dose (VNC13) at diagnosis prior to treatment; subsequent doses: one VNP23 dose at 8 weeks
Influenza	Recommended	Yearly
Hepatitis A	Only if risk factors	1st dose at diagnosis; 2nd dose at 6–12 months
Hepatitis B	Recommended in non-immunized patients	1st dose: month 0; 2nd dose: month 1; 3rd dose: month 6
DTaP (diphtheria, tetanus, and acellular pertussis)	DT booster or DTaP if not previously vaccine against pertussis	–
Human papilloma virus (HPV)	According to vaccine schedule	1st dose: month 0; 2nd dose: month 1 ó 2; 3rd dose: month 6
Meningococcus	Only if risk factors	–

Hepatitis B

HBV screening is particularly important in patients deemed to be at high risk (for instance, those treated with everolimus, temozolomide, rituximab, etc.), and should be assessed in all others, according to the treating physician's clinical judgment. This shall be done by detecting surface antigen (HBsAg), antibody against the hepatitis B core antigen (anti-HBc), and hepatitis B surface antibody (anti-HBs). If everything is negative, there is no infection, the patient should be vaccinated before beginning immunosuppressant therapy. When the HBsAg status is positive, the assessment should include viral load, hepatitis B e-antigen and (HBeAg) determinations, liver function tests and liver biopsy, if appropriate. The results will inform as to whether the patient has chronic hepatitis is in the stage of immunotolerance, or if they are inactive HBV carriers. In the case of chronic hepatitis, they should be given antiviral treatment with entecavir or tenofovir. In the other two scenarios, antiviral prophylaxis should be dispensed.

Negative HBsAg and positive anti-HBc are indicative of resolved hepatitis B. In this case, regardless of the anti-HBs condition, viral deoxyribonucleic acid (DNA) should be assayed. A positive viral load indicates that there is occult infection and preventive treatment given. If the viral load is negative, the possibility of reactivation should be checked regularly throughout the immunosuppressant treatment to detect it early and start treatment as soon as possible. Hepatic biochemistry, HBsAg, and/or viral load are recommended to monitor the patient's status. In high-risk patients, most authors feel that prophylaxis should be initiated directly [4, 5]. When no HBV risk factors are present and the risk of activation of the disease is not to be expected with the oncological therapy to be used, the evidence currently available does not endorse HBV detection prior to initiating treatment against the cancer [6].

There are special situations that are not within the scope of this article.

Tuberculosis

Once the presence of active disease has been ruled out, TBC prophylaxis should be dispensed whenever one or more of the following criteria are met [7–13]: (1) positive (≥5 mm) purified protein derivative (PPD) skin test; (2) positive interferon-γ release assays (IGRA) test; (3) history of improperly treated TBC; (4) radiological findings suggestive of residual TBC lesions, such as apical fibronodular lesions, pleural thickening, etc., or (5) contact with a person with active TBC. The guidelines to be followed are the usual ones with standard precautions.

Central venous line infection

There is currently not enough evidence to support recommending a specific type of indwelling central venous catheter (CVC), be it a tunneled CVC (Hickman), "port-to-cath" (PAC), or a peripherally inserted CVC (PICC). At present there is also insufficient evidence to recommend any insertion site in particular, although femoral access is generally ill advised as it entails a greater risk of infection [14].

The most important measures to prevent CVC infections are: (1) education and training of healthcare professionals; (2) strict washing of the hands, and (3) the use of aseptic techniques when placing and replacing dressings [15]. Routine substitution of the CVC is not advised, nor is application of topical antimicrobials at the site of insertion, since this practice can foster fungal infections and resistances. The use of CVC that are coated or impregnated with antimicrobials/antiseptics, such as chlorhexidine and silver sulfadiazine or minocycline/rifampicin, and/or heparin-impregnated devices can lower the risk of infections, although they are of relative benefit and expensive [16]. It has not been proven that prophylactic administration of antibiotics prior to CVC insertion reduces the incidence of infections [17].

Post-endoscopy infections

Generally speaking, prophylactic antibiotic administration prior to an endoscopic procedure to prevent bacterial endocarditis is not recommended, given that it is infrequent and there is not enough data pointing to a correlation or the usefulness of antimicrobials in this context [18].

In the case of endoscopic retrograde cholangiopancreatography (ERCP), consideration should be give to prophylactic antibiotherapy to cover Gram-negative enteric bacilli and enterococci in patients with obstruction in whom it may not be possible to achieve complete drainage of the biliary tract. Antibiotics should be maintained if the procedure does not resolve the obstruction [18]. In percutaneous endoscopic gastrostomies (PEG), antibiotherapy (cefazolin, 1 g iv; 30 min before the procedure) has been proven to significantly lower the risk of infection [19].

Pneumocystis jiroveci

Prophylaxis against *P. jiroveci* should be contemplated in those who are to receive: (1) temozolamide with radiotherapy; (2) drugs that produce profound T cell lymphopenia, and (3) steroids at a dose equivalent of ≥20 mg/day of prednisone for 4 weeks or more [20].

The regimen of choice is cotrimoxazole (800/160 mg, 1 tablet 3 times per week). In case of allergy to cotrimoxazole, desensitization should be contemplated [21, 22]. Alternatively, atovaquone (1.5 g/day) [23] or dapsone (100 mg/day) can be used. Inhaled pentamidine (300 mg, 4 times per week or monthly iv mensual) is another option [24, 25]. Prevention should be maintained for at least as long as chemotherapy lasts and it is recommended that it be prolonged for at least 2 months or until CD4 lymphocytes are above 200 U/mm^3.

Special situations

Given the current characteristics of the population residing in Spain and the common relations between different geographical areas, *Strongyloides stercoralis* hyperinfestation [26] and Chagas disease (*Trypanosoma cruzi*) prevention [27] should be considered.

Prophylaxis with granulocyte colony-stimulating factors

Preventive granulocyte colony-stimulating factors (G-CSF) administration decreases the incidence, duration, and severity of neutropenia and avoids associated infections [28]. Therefore, the risk of febrile neutropenia (FN) should be estimated prior to initiating chemotherapy, bearing in mind several factors, such as tumor type, the chemotherapy regimen to be used, patient characteristics, or treatment intention. Prophylactic G-CSF is recommended in those in whom the estimated risk of FN surpasses 20 % [29, 30]. If the estimated risk is between 10 and 20 %, each case should be assessed individually, proposing G-CSF mainly if treatment intends to be curative, so as to avoid delays and dose reductions, or in high-risk patients, such as those over the age of 65 years, having had previous episodes of FN, extensive bone marrow involvement, in those who have recently undergone extensive surgery, particularly if it included intestinal resection. Its most controversial preventive use is very advanced tumors, fragile general or nutritional status, significant comorbidities, in whom the benefit of chemotherapy, and even more so, that of maintaining dose intensity is doubtful. Routine use of G-CSF is

not indicated in risk scenarios of less than 10 %, unless there are specific circumstances that entail severe consequences in case of FN.

Treatment with G-CSF in FN shortens hospital stays and time to neutrophil recovery, but is not associated with a benefit in patient survival [31, 32]. G-CSF administration must be contemplated when there is a high risk of complications, for instance in the face of severe neutropenia (neutrophils <100/mm^3) or if expected to be prolonged (>10 days). Likewise, their use should be contemplated in individuals over the age of 65, in cases of sepsis, pneumonia, invasive fungal infection, hospitalization at the time fever appeared, or prior episodes of FN [33].

Antibiotic prophylaxis

People with solid tumors receiving conventional chemotherapy are considered low risk for infectious complications [30]. In this context, fluoroquinolones are somewhat protective [34, 35], but do not lower mortality. In high-risk settings, they have proven to be effective in preventing of infections in neutropenic stages [35], especially in the first cycle of chemotherapy [36]. Given the number of individuals who require preventive treatment, the cost, adverse effects, appearance of superinfections, and selection of resistances [37–42], antimicrobial prophylaxis in low-risk patients on conventional chemotherapy with or without biological agents are not indicated [39, 41]. In specific situations, such as during the first cycle of chemotherapy, when protracted, profound neutropenia can be expected, with highly aggressive cytostatic regimens, when there is high baseline morbidity, or in elderly patients, antibiotic prophylaxis should be decided on a case-by-case basis [43, 44].

Febrile neutropenia

Evaluation of risk of infection in patients with febrile neutropenia

The rate of infectious complications in patients with FN is 25–30 % and mortality is as high as 11 % in some groups [33]. However, this risk is not the same across the board, making overtreatment of low-risk episodes commonplace [45]. Evaluation of risk in these patients seeks to predict the probability of severe complications and, hence, the need for hospital admission and intravenous treatment. Initial assessment should include the following: (1) systemic inflammatory response data, by means of vital signs such as temperature, pulse, and respiratory rate; (2) data regarding severe sepsis, such as hypotension, signs of low tissue perfusion, or of acute organ dysfunction, and (3) existence of primary or secondary focus/foci of infection, within the clinical-epidemiological context.

The most widely validated prognostic tool is the *Multinational Association of Supportive Care in Cancer* (MASCC) scale [46], although it is not specific to cases of solid tumors and in 9–15 % of episodes classified as low-risk, infectious complications can occur [46–48]. Patient selection in clinical trails of oral/ambulatory treatment has been based on pragmatic exclusion criteria with results considered to have been satisfactory [49]. Cases empirically defined as "low risk" are those with neutropenia (<500 neutrophils/mm^3) lasting fewer than 7 days, without complications at first evaluation, and without acute organ dysfunction [49, 50] (Table 3).

The *American Society of Clinical Oncology* (ASCO) recommends avoiding outpatient management in patients with any clinical risk criterion, as summarized in Table 3, regardless of their classification on one or the other risk scale [39]. Moreover, the first prognostic index has recently been published that predicts the incidence of serious complications in patients with solid tumors and apparently stable episodes of FN [51]. The *Clinical Index of Stable Febrile Neutropenia* (CISNE) includes six predictors independently associated with the incidence of serious complications [Eastern Cooperative Group Performance Status ≥2 (2 points), chronic bronchitis (1 point), chronic cardiovascular disease (1 point), mucositis NCI grade ≥2 (1 point), monocytes <200/mm^3 (1 point), and stress-induced hyperglycemia (2 points)]. These factors are integrated into a scale of 0–8, which classifies patients into three prognostic categories: low risk (0 points), intermediate risk (1–2 points), and high risk (≥3 points). The ultimate purpose of this index is to prevent the early discharge of patients who, despite their apparent clinical stability, are at high risk for complications (≥3 points). Other social, psychological, or logistical factors must be taken into account when deciding on treatment modality. Figure 1 presents an action algorithm in caring for patients with FN in the Emergency Department that helps the physician to choose treatment modality.

Febrile neutropenia treatment

While hospitalization and IV treatment of FN have significantly reduced mortality, hospitalization by itself can lead to multiple problems, such as toxicity due to intravenous treatments, increased costs, exposure to nosocomial pathogens and diminished quality of life. This is why individual risk stratification is used to choose hospital or ambulatory treatment strategies.

Empirical antibiotic treatment should be started as soon as possible, given that delaying it can compromise prognosis, after taking blood samples for cultures (if a CVC is

Table 3 Complication risk criteria excluding patients from oral/outpatient management

Category	Severity criteria
Hematologic	Severe thrombocytopenia ($\leq$10,000 cells/mm^3)
	Anemia ($\leq$8 g/dL)
	Thromboembolic disease
Cardiovascular	Hypotension (systolic BP $\leq$ 90 mmHg)
	Clinically relevant arrhythmia
	Acute heart failure
	Chronic cardiovascular disease
	Severe hemorrhage
Digestive–hepatic	Oral intolerance
	Nausea or vomiting
	Diarrhea
	Acute abdominal pain
	Raised transaminases ($\times$5 ULN)
	Bilirubin ($\geq$2 g/dL)
Central nervous system	Acute confusional syndrome
	Meningitis
	Neurological deficit
Infections	Serious infection (pneumonia, intra-abdominal infection, catheter infection, cellulitis $\geq$5 cm, pyelonephritis)
	Signs of sepsis
	Prior antibiotic use ($\leq$72 h previous)
	Allergy to oral antibiotics
Vital signs	Tachycardia, tachypnea, hypotension
Other laboratory data	Hypoxemia, hypercapnia, any clinically relevant abnormality vs. previous analysis
Renal	Dehydration
	Oliguria
	Acute renal failure
	Hydroelectrolytic abnormalities
Other relevant comorbidity	Any serious complication or organ dysfunction contemplated at the start, pregnancy

in place, this is done through the catheter) and of possible sites of infection on the basis of clinical data (urine, sputum, exudate, mucosal or skin lesions mucosas, feces, cerebrospinal fluid, urinary antigens for pneumococcus and/or *Legionella*, nasal swab for the influenza virus during flu season, etc.).

Oral ambulatory treatment

Low-risk patients are candidates for ambulatory treatment, as long as they can tolerate oral administration and have a good socio-family support network. The most widely prescribed combinations are ciprofloxacin with amoxicillin–clavulanic acid and, in cases of allergy to β-lactams, ciprofloxacin with clindamycin. In one multicenter, double-blind, randomized clinical trial, moxifloxacin turned out to be equally efficacious as the amoxicillin–clavulanic acid and ciprofloxacin combination and had fewer gastrointestinal adverse effects [52]. However, moxifloxacin is less active against Pseudomonas and entails greater risk of hepatotoxicity. Patients receiving prophylaxis with fluoroquinolones should not receive empirical treatment with these antibiotics, given the risk that the infection may be caused by bacteria that have become resistant to them.

Individuals who are released with oral ambulatory treatment should be checked 48 h later to verify that their clinical progress is good, monitor microbiology results, attempt to adjust the antibiotic treatment, and define its duration. If there is a deterioration of their clinical status, new diagnostic tests and hospital admission with IV antibiotic treatment should be considered.

IV treatment

High-risk FN patients require hospitalization and parenteral antibiotherapy. Treatment options include antipseudomonal β-lactams, such as piperacillin in combination with tazobactam, cefepime, meropenem, or imipenem

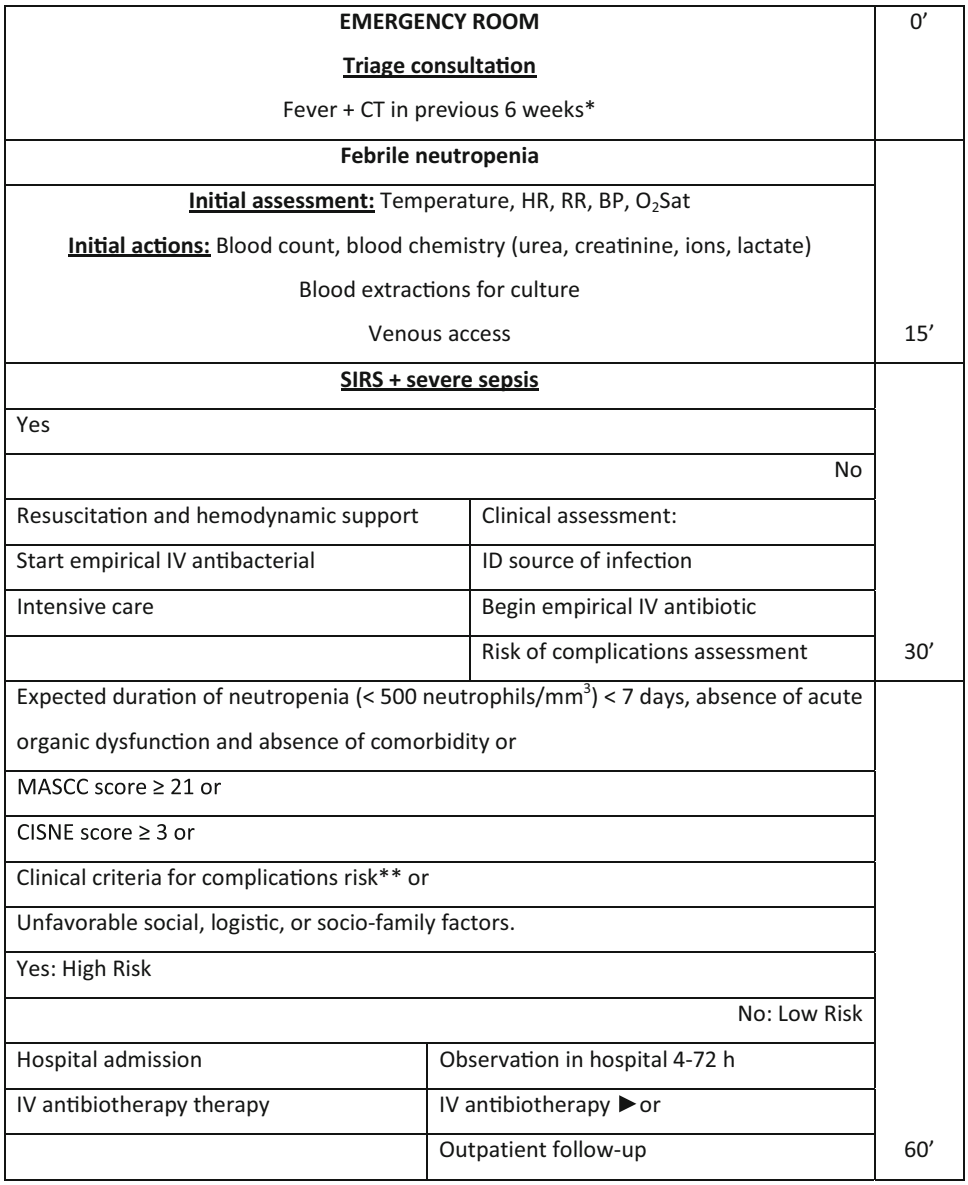

Fig. 1 Action algorithm for initial care for patients with febrile neutropenia at the emergency room and assessment of risk of complications and treatment modality, including maximum desired time for each action

Modified from Bell MS, Scullen P, McParlan D, et al. Neutropenic sepsis guideline. In edition Northern Ireland Cancer Network 2010; 1-11

*No need to wait for laboratory confirmation of neutropenia to start assessment; **Clinical risk criteria: alteration or worsening of organ dysfunction, comorbidity, alteration of vital signs, symptoms or clinical signs, documented focal infection, laboratory or imaging data

HR Heart rate, *RR* Respiratory rate, *IV* Intravenous, *MASCC* Multinational Association for Supportive Care in Cancer, *BP* blood pressure, *CT* chemotherapy, *O_2Sat* arterial oxygen saturation, *SIRS* systemic inflammatory response syndrome, *or* oral route

together with cilastatin. Many centers no long consider ceftazidime in monotherapy to be suitable given its low activity against many Gram-positive microorganisms, such as streptococci. Should the patient be allergic to β-lactams, the alternative is a combination of vancomycin and aztreonam (and with metronidazole if there is an abdominal focus). In individuals who present complications or those in whom infection due to resistant pathogens is suspected, consideration must be given to the use of other drugs, such as aminoglycosides, quinolones, and glycopeptides, and less frequently, daptomycin, linezolid, fosfomycin, tigecycline, and rifampicin. Current scientific evidence reveals that in FN, patient prognosis is not improved with the empirical addition of a glycopeptide to the initial antibiotic regimen [53]. Table 4 presents the doses for the most widely used oral and IV antibiotics.

Table 4 Doses for commonly used oral and intravenous antibiotics

	Doses
Oral	
Amoxicillin–clavulanic	875 mg/q8h
Ciprofloxacin	750 mg/q12h
Moxifloxacin	400 mg/q24h
Levofloxacin	500 mg/q24h
Clindamycin	600 mg/q6h
Intravenous	
Cefepime	2 g/q8h
Ceftazidime	2 g/q8h
Piperacillin-tazobactam	4 g/q8h
Imipenem	500 mg/q6h
Meropenem	1 g/q8h
Amikacin	1 g/q24h
Tobramycin	3 mg/Kg/q24h
Gentamicin	3 mg/Kg/q24h
Ciprofloxacin	200–400 mg/q8–12h
Colistin	4.5 MU/q12h (loading dose 9 MU)
Tigecycline	100 mg/q12h (loading dose 150 mg)
Fosfomycin	2 g/q6h
Vancomycin[a]	1 g/q12h
Teicoplanin	400 mg/q12h × 3 doses, 400 mg/q24h
Daptomycin[b]	10 mg/kg/q24h
Linezolid	600 mg/q12h

MU million units

[a] Adjust dose according to type of infection and microorganism and according to plasma levels

[b] dose may vary depending on infection and microorganism

Empirical treatment strategies in febrile neutropenia

The latest guidelines recently published by the *Infectious Diseases Society of America* (IDSA) recommend the use of an anti-pseudomonal β-lactam in monotherapy as the initial antimicrobial treatment in FN [30]. A meta-analysis found that monotherapy was significantly better than the combination of a β-lactam and aminoglycoside, with fewer adverse effects, lower morbidity, and similar survival rates [54]. In recent decades, we have been witnessing a rise in Gram-negative infections in cancer patients, and in parallel, we are also observing an emergence of multiresistance in these microorganisms [55, 56]. In light of this, there is doubt as to whether initial empirical treatment with a β-lactam in monotherapy is safe enough in FN patients [57].

The ramp-up strategy consists of beginning empirical antibiotic treatment that does not begin by covering resistant pathogens, and, in the event that the patient's condition deteriorates or a resistant pathogen is isolated, treatment is ramped up to a broad-spectrum antibiotic or combination of antimicrobials. The advantages of this approach are that it avoids the early use of broad-spectrum antibiotics, possibly lower toxicity, is more affordable, and entails a less risk of resistance selection, largely carbapenem. In contrast, patients' prognosis may be compromised if the resistant microorganisms are not properly covered from the outset.

The ramp-up scheme should be used in high-risk patients in the following situations: (1) uncomplicated clinical presentation; (2) absence of risk factors for resistant bacteria infection, and (3) in centers having a low prevalence of microorganisms.

The initial treatment options include a non-carbapenemic, anti-pseudomonal β-lactam such as cefepime, ceftazidime, piperacillin, in combination with tazobactam. Carbapenems should be avoided in patients without complications and with no risk factors for resistant bacteria.

In the ramp-down strategy, the antibiotic treatment initially administered covers even the most resistant pathogens. Therapy is later ramped down to smaller spectrum treatment once the presence of resistant pathogens has been ruled out or a pathogen has been identified and its antibiotic sensitivity profile defined. The main advantage of ramping down is that it is more likely to achieve adequate antibiotic coverage at the very beginning. Conversely, this approach results in the often unnecessary use of broad-spectrum antibiotics; physicians tend to not ramp down when they have the chance to do so, and there is a greater risk of resistance selection.

This scheme should be applied: (1) in complicated clinical presentations; (2) when there are risk factors for infection by resistant bacteria, and (3) in those centers with a high prevalence of resistant microorganisms.

Initial treatment options include: (1) monotherapy with meropenem or imipenem in severely ill patients or when there is a prior history of colonization/infection by enterobacteria-producing, extended-spectrum β-lactamases; (2) anti-pseudomonal β-lactam combined with aminoglycoside or quinolone in severely ill patients if the presence of resistant, non-fermenting Gram-negative bacilli (*Pseudomonas aeruginosa* or *Acinetobacter spp.*) is suspected; (3) β-lactam in conjunction with cholistine with or without aminoglycoside, fosfomycin, or tigecycline if infection due to carbapenemase-producing Gram-negative or non-fermenting multiresistant Gram-negative bacilli is suspected, (4) β-lactam coupled with cotrimoxazole if *Stenotrophomonas maltophilia* is suspected. In any case, if risk factors for infection due to a Gram-positive resistant microorganism exist or if infection is severe and related to the vascular catheter or skin or soft tissue, a glycopeptide, daptomycin, or linezolid can be added to the initial therapy.

Table 5 Treatment recommendations for febrile neutropenia when there is a clear clinical focus

Location	Microorganisms	Treatment
Mucositis	*S. viridans*, *S. aureus*, Gram-positive and Gram-negative anaerobes, herpes simplex	Ensure anaerobic coverage
	Candida spp.	If *S. viridans* and highly resistant to penicillin is common in center, add glycopeptide or daptomycin or linezolid
		Consider anti-herpes treatment
		Consider anti-fungal treatment (fluconazole, echinocandin, other azoles)
Esophagitis	*Candida*, herpes simplex virus	Add fluconazole or echinocandin and acyclovir
Neutropenic colitis	Aerobic and anaerobic Gram-negative bacilli, *Clostridium* spp. (typhlitis), *Clostridium difficile*	Ensure anaerobic coverage
		Metronidazole or oral vancomycin if *C. difficile* or dysbacteriosis is suspected
		If previous history of extended-spectrum beta-lactamase (ESBL) or very high incidence in center, add amikacin
Diarrheas	*Clostridium difficile*, Gram-negative bacteria, *Campylobacter* spp., *Salmonella* spp. virus	Add metronidazole or oral vancomycin if *C. difficile* or dysbacteriosis is suspected
Pulmonary infiltrates	*S. pneumoniae*, GNB, *S. viridans*, anaerobic, respiratory viruses, *P. jiroveci*, *M. pneumoniae*, *C. pneumoniae*, *L. pneumoniae*, *Aspergillus*, Nocardia, mycobacteria…	If clinical suspicion of atypical pneumonia, add levofloxacin or azithromycin
		Add oseltamivir during flu season if clinical suspicion
		TMP-SMX if possibility of *P. jiroveci* (prolonged lymphopenia, interstitial pattern, in patients on high doses of corticoids, temozolomide, immunomodulatory agents…)
		If MRSA by previous colonization is suspected, add vancomycin or linezolid
CVC, CIP infection	CoNS, *S. aureus*, *C. jeikeium*, *Bacillus* spp., Gram-negative (*Pseudomonas* spp., *S. maltophilia*), *Candida* spp.	Add glycopeptide (vancomycin, teicoplanin) or daptomycin or linezolid
		Echinocandin or fluconazole if candidiasis is suspected
Cellulitis	CoNS, *S. aureus*, *Streptococcus* spp., *C. jeikeium*, *Bacillus* spp., Gram-negative (*Pseudomonas* spp., *E. coli*, *K. pneumoniae*)	If high incidence of MRSA or previous colonization, add glycopeptide (vancomycin, teicoplanin) or daptomycin or linezolid
		If ecthyma gangrenosum or high incidence of ESBLs in center or known colonization in patient, add amikacin
Urinary infection	Enterobacteriaceae, *Enterococcus* spp., *P. aeruginosa*, *Candida*	If ESBL is suspected, consider betalam with beta-lactamase inhibitor, carbapenem, and fosfomycin
CNS infection and neurosurgery	CoNS, *S. aureus*, *Streptococcus pneumoniae*, *Cryptococcus neoformans,* Herpes simplex virus, *Listeria monocytogenes*	Consider adding linezolid, acyclovir, and ampicillin with/without amphotericin B

CVC, *PICC* central venous catheter, peripherally inserted central catheter, *MRSA* methicillin-resistant *Staphylococcus aureus*, *CoNS* coagulase-negative staphylococci, *CNS* central nervous system, *TMP-SMX* trimethoprim and sulfamethoxazole

Clinical follow-up once empirical treatment has been started

Between 48 and 72 h after initiating empirical treatment, clinical evolution and microbiology should be checked. If the causal agent or clinical focus is isolated, attempts should be made to simplify treatment and adapt it to the sensitivity profile of each microorganism or type of infection, as reflected in Table 5.

In those situations in which no clinical focus or etiological agent has been documented and the patient is stable, antibiotherapy should be ramped down to a more narrow spectrum antimicrobial and/or withdraw the associated drugs (aminoglycoside, quinolone, colistin, etc.). If the initial clinical debut was not severe and the patient has been fever free for more than 72 h and is asymptomatic, the possibility of discontinuing treatment can be assessed. On the other hand, if the patient's condition was initially severe or unstable, the initial antibiotic treatment should not be modified.

In most documented infections, 10–14 days of antibiotherapy suffice. In some cases, treatment can be extended if needed, even after the fever and neutropenia have been resolved. In the event that the catheter is the documented site of infection, the possibility of withdrawing or sealing it with antimicrobials must be weighed, depending on the microorganism isolated and patient characteristics. In individuals with persistent fever, a comprehensive re-

Table 6 Standard precautions and specific precautions depending on infectious disease or microorganism and transmissibility period

Procedure	Examples	Hand hygiene[a]	Gloves[b]	Additional gown	Mask[c]
No contact	Talking to the patient	No	No	No	No
Contact intact skin or unstained clothes	Physical examination, vital signs measurement	Before and after	No	No	No
Contact (or possibility) with non-intact skin, mucous membranes, secretions, excretions	Extractions, dressings, catheter manipulation, catheterization, drains, etc.	Before and after	Yes[b]	No[c]	No[c]
Respiratory secretions	Aspiration, respiratory therapy Tracheotomy dressing	Before and after	Yes[b]	Yes	Yes

Disease or microorganisms	Types of precautions or isolation measures	Probable transmission period
Multiresistant bacterial pathogens (MRSA, VRE, Enterobacteriaceae-ESBL+, *Acinetobacter baumannii*, MDR *Pseudomonas aeruginosa*)	Contact	Cross-species transmission during colonization or infection by corresponding microorganism If prolonged hospital stay, weekly follow-up w/epidemiological cultures for three consecutive weeks; if negative, stop precautions. Short hospital stay: entire hospitalization
Adenovirus	Droplets and contact	Adenovirus infection can be spread for up to 14 days after onset
Influenza	Droplets	3–5 days until the appearance of clinical signs in adults. In children, up to 7 days
Respiratory syncytial virus	Contact	Covers the period immediately prior to active disease and while disease lasts
Parainfluenza	Droplets-fomites	From prior to symptoms until clinical improvement (can be transmitted by asymptomatic carriers)
Measles	Aerial	From 4 days prior to and up to 4 days after rash (minimal contagion after 2nd day of rash)
Rubella (congenital)	Contact	Can spread viruses for months in infants
Rubella	Droplets	From 1 week before to 7 days after rash
Mumps	Droplets	Virus is isolated in saliva from 7 days before to 9 days after overt symptoms begin. Maximum risk of contagion from 2 days before disease onset to 4 days after
Hepatitis A	Contact (fecal-oral)	Infectivity: from 2 or 3 weeks before symptoms until 1 week after onset of symptoms
Rotavirus	Contact (fecal-oral)	During the acute stage, and as long as virus is excreted
Parvovirus B19	Droplets	If only rash, transmissibility peaks before it appears and is unlikely after it disappears. If aplastic crisis, transmissibility is up to 1 week after onset

Table 6 continued

Disease or microorganisms	Types of precautions or isolation measures	Probable transmission period
Varicella zoster	Aerial and contact	4–5 days prior to rash and until lesions have crusted over (±7 days)
Salmonella	Contact (fecal-oral)	First week until end of convalescence (1–2 weeks). In *S. Typhi*, consider chronic carriers
Tuberculosis	Aerial	As long as tubercle bacilli are present in sputum. Efficient antimicrobial chemotherapy eliminates transmissibility at 2–4 weeks
Impetigo	Contact	Until lesions are fully healed (usually 1–2 weeks after)
Mycoplasma (primary atypical pneumonia)	Droplets- recently contaminated fomites or respiratory secretions	<20 days. Treatment does not eliminate microorganism from airways, where it can persist up to 13 weeks
Pertussis	Droplets	Up to 5 days after efficient treatment
Type B *H. influenzae*	Droplets	No longer contagious 24–48 h following the start of efficient antibiotherapy
Neisseria meningitidis	Droplets	Until live meningococci disappear from nasal and buccal secretions, e.g., 24 h after starting appropriate treatment
Scarlet fever	Droplets	Up to 24 days after efficient treatment
Clostridium difficile	Contact	For weeks and months as non-vegetative forms or spores
Scabies (mange)	Contact	Until mites and eggs are destroyed. No transmission 24 h after efficient treatment. (Permethrin 5 %)

ESBL extended-spectrum beta-lactamase, *VRE* vancomycin resistant enterococci, *MDR* multi-drug resistance, *MARS* Methicillin-resistant *Staphylococcus aureus*

[a] Water and soap or aqueous alcohol solution (if no visible dirt)

[b] Must be changed between patients and when going from contaminated to non-contaminated areas; refers to cotton or disposable gown for specific use in procedures, not the usual uniform

[c] Except when dressing wounds

evaluation must be conducted, actively searching for possible foci of infection or other causes of fever, such as drug toxicity, tumor fever, etc.

Biomarkers are analytic parameters that can complement other clinical and microbiological variables in the evaluation of FN, as well as its severity. Likewise, normalization of their values supports the response to treatment. Stress-induced hyperglycemia, as an acute phase reactant, and hypoalbuminemia, as a malnutrition and fragility marker, are the biochemical parameters of greatest interest [47]. The most widely used specific inflammation/infection serum analytes are lactate, procalcitonin, and C-reactive protein. Their usefulness has yet to be determined given the heterogeneity of the populations studied and to the small samples in the clinical trials published [58]. Procalcitonin (value >0.5 ng/ml) is a more useful and earlier marker than C-reactive protein (value ≥90 mg/dl), particularly in diagnosing bacteriemia, since it is not elevated in viral C-reactive protein infections, and in predicting FN severity and complications. The addition of procalcitonin to clinical risk scales enhances sensitivity and negative predictive value to detect bacteriemia and failure of antibiotic treatment [59, 60]. Interleukin-6, 8, and 10 might be better predictors of severity and complications, but are less widely used, given their high cost, lack of availability, and low specificity. Lipopolysaccharide-binding protein, interleukin-2, and tumor necrosis factor, among others, are not currently applied in the context of FN in cancer patients.

Specific precautionary measures

These measures seek to prevent certain pathogens from being spread from one individual who is colonized or has active infection to other patients or to healthcare professionals. One key aspect is that the use of these measures should not affect the quality of care the patient receives; additionally, they should not add to so-called standard precautions, such as washing and decontamination of hands, wearing gloves, gown, and/or mask, depending on the cases, situations, and indications that are shown in Table 6.

Specific precautionary measures are classified according to the microorganism's mode of transmission: (1) respiratory precautions, the aim of which is to prevent dissemination by air of particles >5μ that can remain suspended for long periods of time, as in respiratory TBC, disseminated VZV, measles, etc.; (2) drop precautions that seek to prevent spread of pathogens through larger-sized drops and that require close contact between the exposure source and susceptible host, such as in meningococcus, flu, etc., and (3) contact precautions that attempt to avoid transmission by direct or indirect contact through contaminated objects or surfaces. Table 7 presents the specific recommendations and measures to be adopted depending on the disease or pathogen in question.

Contact precautions are the most frequently needed ones in cancer patients and are indicated in the following situations: (1) respiratory, gastrointestinal, skin infections, and/or wounds infected or colonized by multiresistant pathogens; (2) diarrheic infections, including *Clostridium difficile*; (3) respiratory viral infections, and (4) skin or mucosal infections.

Each center's Infection Commission or Infection Control Team must decide which multiresistant microorganisms are the most important ones and susceptible to the implementation of contact precautions, based on the existing recommendations, and always bearing in mind local epidemiology and the capacity for transmission between patients of each of the multiresistant pathogens appraised. It may be necessary to perform epidemiological surveillance cultures to do so.

Most hospitals recommend the application of contact precautions in the following scenarios: (1) all cases of methicillin-resistant *Staphylococcus aureus*; (2) vancomycin-resistant *Enterococcus*; (3) extended-spectrum beta-lactamase-producing enterobacteriae; (4) carbapenemase-producing enterobacteriae; (5) non-fermenting Gram-negative bacilli, such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii* with patterns of multiresistance or pan resistance.

Inverse isolation measures would be indicated only in those patients with solid cancer who are receiving chemotherapy regimens that lead to profound, protracted neutropenias. Rooms with inverse isolation must have a series of special characteristics that make it possible to decrease environmental contamination forcing microorganism-free air in and preventing pathogens from entering by positive pressure.

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Compliance with ethical standards

Conflict of interest The authors state that at the time of writing and revising the text, they were unaware of the name of the laboratories that have provided economic support for this project, and that said support has, therefore, had no bearing on the content of this article.

Ethical statement The study has been performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent statement Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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