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Update on the infection of the immunocompromised patient

Update on the management of febrile neutropenia in hematologic patients

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ABSTRACT

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 high-risk patient population, since inadequate initial empirical antibiotic treatment can seriously compromise prognosis. Besides, reducing antimicrobial exposure is a cornerstone in the fight against resistance.

Keywords: Febrile neutropenia, hematological disease, empirical antibiotic therapy, targeted antibiotic therapy, antibiotic resistance.

Dr. Gudiol reviewed the most relevant issues included in the recently published 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 [1].

Fever is a common sign in patients suffering from chemotherapy-induced neutropenia, but up to 60%-70% of these patients will not have either an identifiable clinical focus of infection or positive cultures. Gram-negative bacteria are the leading cause of infection in onco-hematological patients with febrile neutropenia (FN) in some institutions, and emergence of multidrug resistance among these organisms is a matter of concern [2]. Overall, more than 50% of the main isolated pathogens in neutropenic patients (i.e., *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*) are resistant to cephalosporins, fluoroquinolones, and aminoglycosides. Carbapenem resistance is rapidly increasing and being identified in up to 50% of *Enterobacteriaceae* isolates in some European countries, and its presence has been described as an independent risk factor for mortality in these patients [3].

Many factors should be considered when choosing empirical antibiotic treatment in patients with FN. These include the risk of infection associated with the severity of neutropenia (low versus high risk), possible focus of infection, clinical manifestations (e.g., hypotension, sepsis, septic shock), local epidemiology, previous infection or colonization by multidrug-resistant organisms (MDROs), previous use of antibiotics, and presence of allergies and potential toxicities. The use of a β-lactam with activity against *P. aeruginosa* is recommended, in monotherapy or in combination with another regimen, according to the clinical presentation and the risk of infection due to MDROs. Therefore, an escalation strategy may be used in uncomplicated clinical presentations, in patients without risk factors for MDROs, and in centers with low prevalence of resistance. Conversely, a de-escalation strategy that ensures early initiation of effective treatment is recommended in severely ill patients, in those with risk factors for MDROs, and in settings with high prevalence of resistance. Piperacillin-tazobactam or a cephalosporin with antipseudomonal activity are preferred for escalation strategy. When choosing the de-escalation strategy, imipenem or meropenem may be chosen, but the combination of an antipseudomonal β-lactam plus an aminoglycoside or fluoroquinolone may also be a suitable option. Addition of amikacin or colistin should be considered if there is a risk of infection due to non-fermenting MDROs, and coverage against MDR gram-positives is indicated in cases of hemodynamic instability or risk of methicillin-resistant *Staphylococcus aureus* infection.

Antibiotic treatment should be selected and modified according to the suspected clinical focus of infection, as shown in Table 1.

Classically, antibiotic treatment was maintained until recovery from neutropenia, but evidence supporting this approach is scare. Furthermore, reducing the exposure to un-

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Table 1 **Empirical antibiotic therapy according to clinical focus of infection**

Entity	Antibiotic treatment
Mild oropharyngeal mucositis	- Cefepime
Moderate-severe oropharyngeal mucositis	- Piperacillin-tazobactam - Imipenem or meropenem
Neutropenic enterocolitis	- Piperacillin-tazobactam - Imipenem or meropenem * Consider treating *C. difficile* if high index of suspicion
Skin and soft tissue infection	- Cefepime - Piperacillin-tazobactam - Imipenem or meropenem +/- - Vancomycin, daptomycin, or linezolid (if history of MRSA colonization/infection) * Consider adding clindamycin if severe necrotizing infection
Intravascular catheter infection	- Cefepime - Piperacillin-tazobactam - Imipenem or meropenem +/- - Vancomycin or daptomycin
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 combination 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 PCR results are received. * Consider the possibility of alternative causes (*Pneumocystis jirovecii*, Cytomegalovirus) in risk patients with bilateral infiltrates.
Urinary tract infection	- Cefepime - Piperacillin-tazobactam - Imipenem or meropenem
Acute meningitis	- Cefepime or meropenem + - Ampicillin * In risk patients with suggestive clinical forms, or space-occupying lesions, consider alternative causes (*Cryptococcus*, *Listeria*, *Nocardia*, filamentous fungi, toxoplasmosis, and *Mycobacterium tuberculosis*)
Meningoencephalitis	Use same treatment as acute meningitis, with adding of Acyclovir

MRSA: methicillin-resistant *Staphylococcus aureus*

Table 2 Exclusion criteria for outpatient oral antibiotic treatment

Patients undergoing allogeneic stem cell transplantation or intensive chemotherapy regimens, for example:
– Intensive induction chemotherapy or high-dose cytarabine (Ara-C) or similar as consolidation treatment for acute myeloid leukemia
– DT-PACE chemotherapy for plasma cell leukemia
– BURKIMAB, DA-EPOCH level ≥3 or Hyper-CVAD chemotherapy for lymphoma
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
Recently admitted to intensive care

necessary antibiotic is a cornerstone in the fight against antimicrobial resistance. In this regard, a multicenter randomized clinical trial (RCT) (the How Long Study) involving high-risk hematologic patients with FN and no etiologic diagnosis to determine the optimal duration of empirical antimicrobial treatment was recently published [4]. 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 following a clinical criterion regardless of the neutrophil count reduced the number of days of exposure to antimicrobials with no impact on mortality, as well as other secondary outcomes (recurrent fever, secondary infections, etc).

In patients with FN and clinically documented infection, antibiotic treatment can be discontinued when clinical signs and symptoms of infection have resolved and the patient remains afebrile for at least 72 hours. If infection has been microbiologically documented, a minimum of 4 days of apyrexia and 7 days of antibiotic treatment are recommended to stop antibiotic treatment. Neutrophil recovery is not a necessary precondition to determine length of antibiotic treatment.

Special attention was given to the treatment of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E). In this regard, the use of β-lactam/β-lactamase inhibitor (BLBLI) combinations as carbapenem-sparing alternatives is a matter of debate. The recently published MERINO trial, failed to demonstrate the non-inferiority of piperacillin-tazobactam compared to carbapenems for the treatment of bacteremia due to cephalosporin-resistant *Enterobacteriaceae*, in terms of overall 30-day mortality [5]. Nevertheless, the study did have some limitations. Of note, a retrospective multicenter international cohort study involving neutropenic high-risk hematologic patients with bacteremia due to ESBL-E (the BICAR study) found no differences in 7, 14 or 30-day mortality rates among patients treated with BLBLI combinations or carbapenems, either as an empirical or a definitive therapy, and after performing a propensity score analysis [6]. Therefore, BLBLI combinations (mainly piperacillin-tazobactam) should be considered as carbapenem-sparing alternatives for the treatment of low-risk patients who do not have a high-inoculum infection and present without severe sepsis or septic shock. Optimized dosing and extended infusion is strongly recommended. In this regard, a recently published RCT involving hematologic patients with FN showed significant better clinical outcomes in patients receiving the empirical β-lactam antibiotic in extended infusion compared with those who received it in bolus [7].

Patients considered to be at low risk for complications can be treated with oral antibiotics and outpatient follow-up after 48-72 hours [8]. Stratification of patients should include validated models such as the MASCC index score [9]. Contraindications for this strategy are signs or symptoms of hemodynamic instability, localized infection, oral intolerance, new clinical signs and symptoms, or isolation of microbiological species non-susceptible to initial empirical therapy. Antibiotic treatment should include a fluoroquinolone with antipseudomonal activity, plus an agent with Gram-positive cocci activity (e.g.: amoxicillin/clavulanate or clindamycin); cefuroxime or cefixime in combination with ciprofloxacin may be an alternative. Fluoroquinolones should be not used empirically if the patient has received these antibiotics as a prophylaxis regimen. Table 2 shows the exclusion criteria for outpatient oral antibiotic treatment.

Finally, antibacterial prophylaxis was also addressed. Due to the high prevalence of quinolone resistance among Gram-negatives, and the risk of resistance development in several Gram-positive and Gram-negative organisms, universal prophylaxis with quinolones is not recommended for low-risk

patients. Individual evaluation for its use should be performed in high-risk patients with profound and prolonged neutropenia. Centers performing fluoroquinolone prophylaxis should implement active monitoring strategies for emergence of resistance.

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