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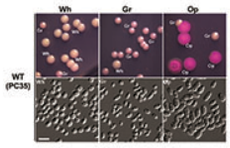

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REVIEW

Bloodstream infections in neutropenic cancer patients: A practical update

Giulia Gustinetti and Malgorzata Mikulska

Division of Infectious Diseases, University of Genova (DISSAL) and IRCCS San Martino-IST, Genova, Italy

ABSTRACT
Bloodstream infections (BSI) are among the most frequent complications in neutropenic cancer patients and, if caused by Gram-negative rods, are associated with high mortality. Thus, fever during neutropenia warrants prompt empirical antibiotic therapy which should be active against the most frequent Gram-negatives. In the last decade, there has been a worldwide increase in multidrug resistant (MDR) strains. In these cases, the traditional choices such as oral therapy, ceftazidime, cefepime, piperacillin-tazobactam, or even carbapenems, might be ineffective. Therefore novel de-escalation approach has been proposed for patients who are at high risk for infections due to MDR bacteria. It consists of starting antibiotics which cover the most probable resistant strain but it is narrowed down after 72 hours if no MDR pathogen is isolated. With increasing bacterial resistance, the benefit of fluoroquinolone prophylaxis during prolonged neutropenia remains to be confirmed. Antibiotic stewardship and infection control programs are mandatory in every cancer center.

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Introduction

Compared to previous decades, the management of neutropenic cancer patients is nowadays particularly challenging, because of the adoption of intensive chemotherapy protocols, widespread use of monoclonal antibodies or other biologic agents, the increasing age of cancer patients and frequent presence of multiple comorbidities. Thus, even if the overall survival in cancer population has improved, clinicians are frequently faced with infectious complications. Low granulocyte count, mucosal damage and the presence of central venous catheters (CVC) expose patients to the risk of bacterial infections, especially shortly after chemotherapy, while prolonged neutropenia is a classic risk factor for mold diseases. The spectrum of infections associated with novel biological therapies is constantly expanding, as these agents might be associated both with the worsening of immune deficits caused by traditional chemotherapy and with specific infectious risks.

Bacterial bloodstream infections (BSIs) rank first in terms of infectious complications during neutropenia and the inadequacy of the inflammatory response makes sepsis a significant cause of death in this setting.[1] Therefore, febrile neutropenia should be considered a medical emergency and a prompt administration of empirical antibiotic therapy is mandatory, since it has been associated with lower morbidity and mortality.[2-4] Definitions of BSIs, sepsis, neutropenia and fever are reported in Table 1.[5-8]

In the last decade, a worldwide increase in multidrug resistant (MDR) strains has occurred and numerous initiatives have tried to draw public attention to the fact that there are bacteria against which few or no active antibiotics exist.[9-11] The acronym ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.) summarizes the most threatening pathogens circulating today.[9-11]

Antimicrobial resistance is reported according to the clinical breakpoints recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the Clinical and Laboratory Standards Institute (CLSI) or the US Food and Drug Administration (FDA). Various definitions of MDR pathogens have been used, but a joint initiative by the European Center for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) expert panel defined multidrug resistance as acquired non-susceptibility to at least one agent in 3 or more antimicrobial categories which are relevant for a given species.[12] In general, Gram-negative (GN) bacteria are reported as MDR if not susceptible to at least 3 of the

CONTACT Malgorzata Mikulska m_mikulska@yahoo.com Division of Infectious Diseases, University of Genova (DISSAL) and IRCCS San Martino-IST, Largo R. Benzi 10, Genova 16132, Italy.
On behalf of the European Study Group on Infections in the Immunocompromised Host (ESGICH-ESCMID).

Table 1. Definitions of clinical situations referred to in the text.

	Definition
Antibiotic prophylaxis	Administration of antibiotics to patients without any signs or symptoms of infection with the aim of preventing infectious complications
Bloodstream infection (BSI)	A laboratory-confirmed positive blood culture which can be the consequence of an infection at other body sites (secondary BSI) or not (primary BSI). In case of potential common skin commensals such as coagulase-negative staphylococci, *Corynebacterium* species other than *C. dyphteriae*, *Bacillus* species other than *B. anthracis, Micrococcus*, etc., at least two consecutive positive blood cultures, drawn in different occasions, are needed [7]
Catheter-related bloodstream infection (CLABSI)	BSI and clinical manifestations of infection in presence of an intravascular device with > 1 positive blood culture from a peripheral vein and no other reliable sources of infection. One of the following should also be present: a positive semiquantitative or quantitative catheter culture; blood culture obtained through catheter positive at least 2 hours earlier than the blood culture drawn peripherally at the same time; quantitative cultures of blood with a ratio of 3:1 cfu/mL of blood (catheter vs. peripheral blood) [84]
Colonization	Presence of bacteria on body surfaces, such as skin or mucosae, without invading or damaging the tissue and without an immune reaction
Empirical antibiotic therapy	Antibiotic treatment given in case of suspected infection before microbiology results are available; the knowledge of the bacteria commonly involved and local epidemiology drive the empirical choice of the drug(s)
Fever	A single oral temperature ≥ 38,3°C (101°F) or as a temperature above 38.0°C (100.4°F) for at least one hour [8]
Mucosal-barrier injury CLABSI (MBI-CLABSI)	Blood culture positive for one of the following intestinal organisms such as Enterobacteriaceae, viridans streptococci, *Bacteroides* spp., *Enterococcus* spp., *Fusobacterium, Peptostreptococcus, Prevotella* or *Clostriudium* in a neutropenic patient or in a HSCT recipient with severe gastrointestinal graft-versus-host disease or diarrhea [7]
Multidrug-Resistant Gram Negative bacteria	Bacteria which are not susceptible to at least three of the following antimicrobial categories: antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides and fluoroquinolones [13]
Neutropenia	A granulocyte count < 500 cells/μL or < 1000 cells/μL with an expected decline greater than or equal to 500 cells/μL over the next 48 hours [5]
Sepsis	A documented or suspected infection plus some of the following criteria: • General parameters: Fever (core temperature > 38.3°C, hypothermia (core temperature < 36°C), Heart rate > 90 or > 2DS the normal value for age, Tachypnea > 30, Altered mental status, Significant edema or positive fluid balance, Hyperglycemia (plasma glucose > 110 mg/dl) in the absence of diabetes. • Inflammatory parameters: Leukocytosis (WBC > 12000 cell/μL), Leukopenia (WBC < 4000 cell/μL), Normal WBC with > 10% of immature forms, CRP or PCT > 2 SD above the normal value. • Hemodynamic parameters: Arterial hypotension (systolic blood pressure < 90 mmHg, mean arterial pressure < 70 mmHg, Systolic blood pressure decrease > 40 mmHg or < 2SD below normal for age, Mixed venous oxygenation > 70%, Cardiac index > 3.5 L/min × m2, • Organ dysfunction parameters: Arterial hypoxemia (PaO2/FiO2 < 300), Acute oliguria (output < 0.5 ml/kg × min), Creatinine increase > 0.5 mg/dL, Coagulation abnormalities (international normalized ratio > 1.5, Activated partial thromboplastin time > 60 s), Ileus, Thrombocytopenia (< 100,000/μL), Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L) • Tissue perfusion parameters: Hyperlactatemia (> 3 mmol/L), Decreased capillary filling or mottling.

following antimicrobial categories: antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides or FQs.[13] Among Gram-positives (GP), methicillin-resistant staphylococci, and vancomycin-resistant enterococci (VRE) are usually considered MDR pathogens.[14]

The universal increase of resistant bacteria in cancer patients has important consequences for the choice of an effective empirical therapy or prophylaxis.[15,16] In many centers, Enterobacteriaceae are no longer susceptible to cephalosporins, and, in extreme cases, the lack of drugs active against carbapenem-resistant GN rods forced clinicians to choose combination therapies based on old, frequently toxic molecules such as polymixins. Moreover, the benefit of the prophylaxis with fluoroquinolones (FQs) in settings with high FQs-resistance rates has been questioned.[17,18] Finally, healthcare costs are increased in case of infections with resistant bacteria due to prolonged hospitalization and expensive antibiotic treatments.[19,20]

Fluconazole prophylaxis has significantly reduced infections caused by *Candida* spp, making *Aspergillus* the most frequent fungal pathogen during prolonged neutropenia.[21,22] Thus, fungal bloodstream infections,

which are predominantly caused by yeasts, will not be discussed in this paper.

This review will focus on BSIs occurring during chemotherapy-induced neutropenia and it will offer a practical update on the epidemiological data, risk factors and management issues.

Incidence of febrile neutropenia

Fever developing during neutropenia is a frequent complication in neutropenic cancer patients, affecting 80% of those with hematological malignancies and 10–50% of those with solid malignancies.[8,23] Its incidence in solid metastatic cancers was estimated to be about 13–21%, depending on the underlying disease, and occurred mostly during the first chemotherapy cycle.[24] The possibility of BSIs is the major concern at the onset of fever, since it accounts for 10–25% of all febrile episodes in neutropenic patients, with an incidence as high as 13–60% in haematopoietic stem cell transplantation (HSCT) recipients.[8,25] Moreover, the occurrences of severe sepsis and septic shock in the setting of febrile neutropenia have been estimated to be, respectively, 20–30% and 5–10%.[26-28]

Epidemiology of bacterial BSI

Increase in gram-negatives

Trends in global epidemiology of BSIs in neutropenia were characterized by the prevalence of Gram-negative bacteria in the 1960s and 1970s, but, starting from the mid-Eighties, Gram-positive strains became predominant.[29-31] That shift was probably caused by widespread administration of FQs prophylaxis, the almost universal use of CVCs and by chemotherapy regimens associated with severe mucositis.[31] In fact, in 2000 GP bacteria accounted for 76% of all BSIs in cancer patients in the United States.[29] However, this tendency has reversed again, with GN bacteria becoming more frequent than GP in many centers.[32-38] According to a questionnaire survey performed among hematology centers from Europe and Israel participating in the European Conference on Infections in Leukemia (ECIL) in 2011, Enterobacteriaceae were isolated in approximately 30% (range 8–56%) of the BSIs, followed by coagulase-negative staphylococci (24%, range 7–51%).[39] The GP to GN ratio was 55% to 45%, but a large variability between hospitals and countries has been noted.[39] Similarly, in a recent systematic review on febrile neutropenic patients, blood cultures were positive for GN rods in a percentage ranging from 25% to 74% (mean 49%), and *Escherichia coli* was the most frequently isolated pathogen.[40] There are even cohorts in which *Pseudomonas* spp. and *Acinetobacter* spp were responsible for 43% of all sepsis episodes.[41]

The issue of polymicrobial BSIs is likely underestimated, partially because of the lack of a common definition, but it is probably applicable to the 8–32% of total BSI cases.[42]

Increase in resistant strains

Following worldwide changes in bacterial susceptibility, also cancer population witnessed an important increase in infections caused by resistant strains.[16,43,44] Similarly to what noted for general population, the rate of MDR bacteria among neutropenic patients seems to increase from north/west to south/east European countries.[11,39] However, as demonstrated for carbapenem-resistant Enterobacteriaceae, in many countries with relatively low prevalence of this resistance pattern, interregional spread of resistant strains has occurred.[45] On the other hand, there are still regions where resistant strains are infrequent and the mortality associated with BSIs remains low.[46] Therefore, a continuously updated knowledge of local epidemiology is crucial.

ESBL-producing Enterobacteriaceae

Extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae, which might not be covered by the standard empirical therapy with cephalosporins or piperacillin-tazobactam, are increasing in frequency in the neutropenic cancer patients[36,37,39,47,48] The percentage of ESBL-producing *K. pneumoniae* strains was over 50% in several series, while it was lower for *E. coli*, varying between 11% and 69% in different countries, even in pediatric patients.[37,49-51] For example, ESBL-producing strains accounted for the 26% of all the *E. coli* and *K. pneumoniae* isolates in neutropenic patients in a South Korean study and for approximately 40% in Italian cohorts[36,43,49,52]

Carbapenem-resistant gram-negative bacteria

Carbapenem-resistance among GN bacteria is rising worldwide, different resistance mechanisms underlie non-susceptibility to this class of β-lactams, and *K. pneumoniae, E. coli, P. aeruginosa* and *A. baumannii* are the most affected species.[45,53] In consequence, in many countries, also cancer patients develop carbapenem-resistant infections, as demonstrated by a retrospective survey performed in 52 transplant centers in Italy.[54] In fact, in HSCT patients the incidence of carbapenem-resistant *K. pneumoniae* infections showed a 6-fold increase between 2010 and 2013, reaching the rates of

0.5% in autologous transplant and 2.9% in allogeneic transplant settings.[54] In a monocentric retrospective observational trial performed in Turkey, carbapenem-resistant GN were isolated in 9% of all the bacteremic episodes during neutropenia.[34] Of note, rectal colonization by carbapenem-resistant *K. pneumoniae* was followed by BSIs in 45% of neutropenic patients.[55]

Also non-fermenting GN rods harbor frequently this type of resistance. In fact, *P. aeruginosa*, which is responsible for 15–20% of GN infections,[56] might be frequently carbapenem-resistant in some regions, as demonstrated in an Italian multicenter cohort, where 71% of strains were MDR.[32] In other regions, as reported by studies from India or South Korea, *A. baumannii* has emerged as a common pathogen isolated in BSIs in neutropenic patients, and it is frequently resistant to cephalosporins or carbapenems.[41,57]

Resistant gram-positives

The antimicrobial resistance among GP bacteria, which involves resistance to methicillin in staphylococci and to vancomycin in enterococci, has been already reported for almost 2 decades, but it is less problematic compared to MDR GN bacteria since novel antibiotic options exist. Nevertheless, the rate of methicillin-resistant coagulase-negative staphylococci is reported very high in cancer patients, with over 60% of European ECIL centers reporting more than 50% resistance rate.[39] *S. aureus* is by far less common cause of BSIs in hematology patients (approximately 5% of all BSI), but is also frequently resistant to methicillin.[39] Fortunately, for reasons which yet remain to be fully established, since 2004 a steady worldwide decline in the incidence of infections caused by methicillin-resistant *S. aureus* (MRSA) has been noted in the US and in several European and Far East countries, despite different infection-control approaches undertaken.[11,58] As far as enterococci are concerned, *E. faecium* has replaced *E. faecalis* in frequency in some centers,[36] and this change is associated with a greater risk of resistance to penicillin and to vancomycin.[47]

Outcome

In general, mortality rates in neutropenic patients with BSIs have largely decreased from 25% in late 1970s to 6% in recent years,[59] but a rise in MDR GN rods may hamper this achievement, as already reported in several studies.[60-62]

Usually, GP BSIs result in a lower mortality than GN ones,[43,63,64] yet the mortality rate is very variable. For instance, it can range from 4% in infections caused by coagulase-negative staphylococci to 40% in a MRSA outbreak involving early post-HSCT patients.[65,66] Viridans group streptococci (VGS) can be responsible for life-threatening infections in neutropenic patients, even though VGS are often susceptible to penicillin. Indeed, VGS bacteremia can be complicated by an acute respiratory distress syndrome (ARDS) in 18–39% of cases, with a mortality rate of 20%.[67-69] Usually enterococcal BSIs are related to poor underlying clinical conditions, and their direct impact on mortality is unclear[70,71] In some centers, infections with VRE strains have been associated with a higher mortality rate than in case of susceptible strains (33–79%).[58,72] However, the role of resistance to vancomycin in increasing the mortality of enterococcal infections remains elusive. In fact, in a Brazilian study performed in 100 hematology patients who were colonized with VRE, the empirical treatment of neutropenic fever with linezolid had no effect on survival, while in a Korean cohort of neutropenic patients, a delayed use of adequate antibiotics in case of VRE infection resulted in no difference in 30-day mortality compared to infections caused by vancomycin-susceptible strains.[73,74] In fact, the persistence of neutropenia, the presence of graft-versus-host disease and the severity of the underlying disease were the only independent predictors of mortality.[73,74]

Patients with infections caused by resistant GN are less likely to receive an adequate empirical treatment, which in turn results in higher mortality rates, both in general population and in the setting of cancer patients.[48,52,75] Indeed, a prospective observational study carried out in Spain revealed higher mortality in neutropenic patients with BSIs due ESBL-producing Enterobacteriaceae who received an inadequate empirical treatment compared to those receiving appropriate therapy (37.5% vs. 6.5%).[48] High mortality rates were found for ESBL-producing *E. coli* (19%) and *K. pneumoniae* (29%) in cancer patients in Taiwan as well.[76] Also in an Italian cohort of hematology patients, infections caused by ESBL-producing isolates were associated with an almost 9-fold increase in mortality.[52] Similarly, in a recent study in neutropenic patients in Lebanon, infections with resistant bacteria were associated with a higher rate of intubation, sepsis and mortality; in particular, these outcomes were 4-fold higher in infections caused by strains resistant to 3rd generation cephalosporins compared to susceptible ones, and 10-times higher in MDR infections compared to non-MDR ones.[77]

Indeed, MDR *K. pneumoniae* showed a mortality rate of 69% in a small cohort of 14 bacteremic patients with hematologic malignancies,[44] and such a poor outcome was also reported in allogeneic HSCT recipients.[54] Also another small study from Turkey demonstrated a fatality

rate of 50% for carbapenem-resistant GN in neutropenic patients.[34]

Finally, the mortality rate was also found to be increased in polymicrobial BSIs compared to monomicrobial infections (19% vs. 12%; p= 0.07).[43]

Risk factors for BSI during neutropenia

In patients experiencing neutropenia the occurrence of BSIs is influenced by several risk factors such as mucositis, the presence of CVC, gastrointestinal bacterial colonization, prolonged hospital stay, acute myeloid leukemia and previous antibiotic treatments.[8,78]

Mucositis

The damage of the mucosal barrier is the result of standard-dose chemotherapy and radiotherapy, and is usually the most pronounced in the small intestine. The underlying mechanisms have been partially identified and the release of pro-inflammatory cytokines and tissue enzymes (such as matrix metalloproteinases or sphyngomyelinases) results in apoptosis and tissue injury.[79] Mucosal barrier injury and ulcerations allow bacterial translocation which has been proved to increase the incidence of bacteremia.[80] Mucositis caused by chemotherapeutic agents or by total body irradiation, along with the prophylaxis with either FQ or trimethoprim-sulfamethoxazole, are considered the most important risk factors for VGS BSIs.[81,82] It has been recently demonstrated that mucositis, rather than prolonged neutropenia, was responsible for a high rate of bacteremia in HSCT recipients.[83] By comparing the levels of citrulline, a biomarker of mucosal damage, it was established that only patients undergoing myeloablative conditioning developed hypocitrullinemia, which corresponded to severe mucositis, and had higher risk of BSIs (44% vs. 11%; $p < 0.001$), compared to patients undergoing non-myeloablative conditioning, despite the longer duration of severe neutropenia in the latter group.[83]

Central venous catheters

The CVC insertion is often necessary both for the administration of chemotherapeutic agents and for supportive therapies. The definition of CVC-associated BSI is reported in Table 1.[84] The presence of a central line increases the likelihood of sepsis and the risk appears to be greater with multiple-lumen devices, in patients with hematological malignancies, and in case of numerous CVC manipulations.[85] There are experiences demonstrating that the incidence of CVC-associated BSIs in neutropenic patients could be significantly reduced (e.g. from 24.3 to 16.2 per 1000 neutropenic days) by targeted educational and training activities.[86]

Peripherally inserted central catheters (PICC) are commonly employed in cancer patients and in 2 cohorts the incidence of PICC-related BSIs was very low (0.05 per 1000 catheter days), although the incidence of localized PICC-associated infections and thrombosis was high.[87,88]

Although CVC is associated with an increased risk of BSI, in neutropenic patients most of the infections are caused by translocation of intestinal bacteria. It has been estimated that approximately 40–50% of bloodstream infections in oncologic settings are due to mucosal barrier injury.[89] Therefore, in a recent manual on Central Line-Associated Blood Stream Infections (CLABSI), the definition of Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection (MBI-LCBI) has been introduced as reported in Table 1.[7]

Others

Other risk factors for BSIs during neutropenia are the length and the severity of neutropenia.[90,91] In fact, in case of allogeneic HSCT, some types of donors, such as unrelated and cord blood, were associated with higher rate of BSI, probably because of longer pre-engraftment neutropenia, compared to peripheral blood as a stem source.[92] Male sex and advanced acute myeloid leukemia were found to increase the risk of BSIs in peripheral blood stem-cell transplantation in a large German study, while another cohort confirmed higher risk of BSI in case of acute leukemia and prolonged hospital stay, but found the opposite effect of the gender (higher BSI risk in females).[78,93] The presence of relapsed malignancy was also associated with an increased risk of bacteremia in a large study of pediatric cancer patients.[94]

Fecal colonization with resistant strains is related to an increased probability of BSIs caused by the same bacteria and the relative risk ranged from 3.4 to 4.5 for ESBL-producing *E. coli*.[95,96]

Prophylaxis of bloodstream infection and fever during neutropenia

Isolation of neutropenic patients in single rooms, observance of contact precautions and basic hygiene procedures are essential, but not sufficient, steps in infections prevention. Chemoprophylaxis is defined as administration of antibiotic agents to patients at risk for infectious complications but without any suggestive signs or symptoms, in order to prevent bacterial infection (Table 1).

The benefit of antibiotic prophylaxis has been always debated but the current European and American

guidelines recommend FQ prophylaxis when the duration of neutropenia is expected to be longer than 7 days.[5,8,97-99] On the contrary, the Australian Consensus Guidelines recommend to consider the use of prophylaxis only for outpatients receiving HSCT and in palliative care patients with bone marrow failure.[18] All these recommendations are based on the results of 2 large randomized, double-blinded and placebo-controlled trials, published in 2005, which assessed the efficacy of levofloxacin during neutropenia in patients undergoing chemotherapy for solid cancers or acute leukemia.[100,101] Although both of them reported a significant reduction in febrile episodes and infections, no survival benefit was observed.[100,101] Only when these results were included in a meta-analysis together with previous studies, a statistically significant reduction in mortality was reported.[102] Since few studies have been performed in the last decade, an update of this meta-analysis did not report any significant changes.[103] Of note, 2 recent meta-analyses, one involving exclusively HSCT recipients (over 1400 patients, mostly after autologous HSCT) and the other including only randomized placebo-controlled and blinded studies failed to show significant survival benefit of FQ prophylaxis.[104,105]

Moreover, there are growing concerns about a worldwide increase in resistance to FQs, and, consequently, the efficacy and ecological impact of FQ prophylaxis. Resistant GN are frequent in the intestinal flora of patients receiving FQs prophylaxis, and FQs were linked to the proliferation of MRSA, *C. difficile*, VRE, and ESBLs.[18,106] A comprehensive cancer center in the United States documented a rising proportion of FQs-resistant *E. coli*, from less than 15% in the 1990s to 46% in 2009.[107] The data on FQs resistance have led some centers to discontinue prophylaxis, and most of the cohorts reported no increase in the mortality, despite an increase in BSIs in some of them.[33,108,109]

The use of drugs to prevent GP infections during neutropenia is currently not recommended. A single-center observational study demonstrated that vancomycin-based prophylaxis (alone or in combination with FQs) was able to prevent VGS bacteremia in HSCT recipients (0 cases per 1000 patients-days) when compared with no prophylaxis or FQs alone, although no data on mortality were available.[81] Given low risk of mortality associated with GP infections, any effect on survival is unlikely.

Single center experiences with other systemic antibiotics used for prophylaxis failed to report any significant benefit on mortality, and are currently discouraged in the attempt of limiting antibiotic pressure.

Non-antibiotic prophylaxis of febrile neutropenia is based on the use of granulocyte colony-stimulating factors (G-CSFs) or granulocyte-macrophage colony-stimulating factors (GM-CSFs) which are administered to prevent or shorten the length of neutropenia. According to international guidelines, these agents should be used only when the predictable risk of febrile neutropenia associated with the specific chemotherapeutic regimen is greater than 20%.[110,111] In patients with intermediate risk (10–20%), other risk factors should be taken into consideration (age of 65 y or older, prior febrile neutropenia, advanced disease, etc.).[111] Although G-CSF administration, particularly after solid tumor chemotherapy, reduces the rate and length of neutropenia and consequently the probability of developing febrile neutropenia, the impact on mortality has not been demonstrated.[112,113]

Infection control and decolonization

In the era of MDR pathogens, the prevention of infections due to these strains is particularly important. Since colonization is the main risk factor for subsequent infection with resistant bacteria, prevention of initial colonization by applying infection control measures is crucial and should be pursued in every cancer center.[114] The main elements of infection control program are outlined in Table 2. Problem recognition is fundamental for choosing effective strategies to prevent nosocomial transmission, thus active surveillance for resistant pathogens should be performed.[114] Of note, control of resistant organisms is a national and worldwide problem and requires that facilities which share the same patients work together to prevent transmission of resistant pathogens.

Once colonization with a MDR strain occurs, the risk of subsequent infection is particularly high in neutropenic patients. For carbapenem-resistant Enterobacteriaceae, rectal colonization by resistant pathogens was followed by BSIs in 45% of neutropenic patients.[55] The association between colonization and subsequent infection has been reported for many MDR bacteria, such as VRE, ESBL-producing Enterobacteriaceae, *P. aeruginosa, S. maltophilia* and carbapenem or colistin resistant *K. pneumoniae*.[115,116]

Therefore, decolonization before the onset of neutropenia seems appealing in case of carbapenem-resistant bacteria, but very few data on the efficacy of this approach exist in this setting. For this purpose, oral gentamycin or a combination of oral gentamycin and colistin were used, with eradication rate of 40–50%, which was higher than the spontaneous eradication rate, but tended to decrease after few weeks.[117-119] The efficacy of decolonization was significantly lower in case of concomitant administration of systemic antibiotic therapy, which is frequently the case in cancer population.[117] The main drawback of decolonization is the possibility of

Table 2. The main elements of infection control program.

Main elements	Necessary actions	Practical aspects
Problem recognition	Knowledge of local epidemiology	Reporting regularly the most frequent resistance patterns and the mortality according to these patterns
	Active surveillance for selected resistant bacteria (e.g. MRSA, VRE, CRE, ESBL-E)	Establishing the need for active screening (e.g. only at admission in patients coming from countries with high rate of MDR bacteria, weekly if local transmission is possible, etc.)
	Alerts from microbiology when new MDR bacteria are isolated in the center	Swift reporting from microbiology to clinicians Rapid identification of any nosocomial transmission
	Reporting data on patient's colonization status	Communication of colonization status of infected and colonized patients at discharge or transfer Identifying known MDR carrier patients at re-admission
Infection control measures	Hand Hygiene	Train all staff in hand hygiene Provide access to hand hygiene stations Monitor adherence and provide feedback
	Antiseptic whole body washing and decolonization	The efficacy of chlorhexidine bathing and nasal decolonization has been only reported for MRSA Chlorhexidine bathing is recommended by some guidelines for CRE carriers
	Contact Precautions	Patient isolation in a single room (preferred option) or patient cohorting Staff cohorting if necessary Use of disposable gloves and gowns Clear guidelines for discontinuation of contact precautions
	Antimicrobial stewardship	Optimizing the use of available antibiotics (right dose, right indication) Preferring narrow-spectrum agents Avoiding prolonged treatment courses

inducing or selecting resistance to the last antibiotics which could be administered in case of the MDR infection. In fact, in 2 of the studies the rate of post-decolonization resistance was 25% and 45% to gentamycin and 40% to colistin.[117,118] Finally, digestive decontamination is not applicable to patients colonized in organs other than gastrointestinal tract. Unless we have more data in neutropenic subjects, or novel therapeutic options are available, decolonization will remain a controversial procedure to be carefully considered for selected patients.

Initial management of febrile neutropenia

Diagnosis

Blood cultures are the cornerstone of diagnostic workup of febrile neutropenia, as they provide pathogen identification and susceptibility pattern. Since their sensitivity is significantly lower once antibiotic therapy has been started, they should be performed immediately when infection during neutropenia is suspected.[120] Hopefully, novel diagnostic methods, mostly based on Polymerase Chain Reaction (PCR) systems, will improve the yield of blood cultures, particularly if drawn after the onset of antibiotic therapy, such as in case of persistent fever, and will result in shorter time to microbiological diagnosis.[120] Furthermore the combination of nucleic acids amplification with mass spectrometry could permit obtaining the results within 6 hours, but no data are so far available in hematology or oncology settings.[121]

In non-neutropenic patients, procalcitonin (PCT) is used as an early serum marker of inflammation (it increases within 3 hours from infection, compared to 24 hours for C-reactive protein, CRP), as it has over 90% sensitivity and specificity for bacterial BSI.[122] However, in neutropenic patients with sepsis, neither PCT nor CRP differed significantly between patients with and without an infection, thus they seem to offer little help in early differentiation between bacterial infection and inflammation in this population.[123]

Assessment of risk for a severe or complicated infection

Neutropenic patients with suspected infection should be initially evaluated for a possibility of a complicated course of infection. Several clinical scores summarize the main parameters to be assessed. The Multinational Association for Supportive Care in Cancer (MASCC) risk index score is a simple algorithm which helps clinicians to evaluate the risk and to determine if hospital admission is mandatory or outpatient management might be an option.[124] The predictive positive value ranges from 83% to 98%, even though only a small proportion of hematologic patients were included in validation studies.[125,126] The Clinical Index of Stable Febrile Neutropenia (CISNE) score has also been recently proposed for severity evaluation in neutropenic patients with solid tumors and it showed better sensitivity and specificity in this setting when compared to MASCC score.[127] The elements evaluated for risk assessment according to the aforementioned scores are reported in Table 3. Although the use of MASCC score is advised by numerous

Table 3. Clinical data at onset of febrile neutropenia which allow for calculating the risk for severe complications in cancer patients.

MASCC SCORE		CISNE		
Clinical Parameters	Score	Eligibility criteria	Clinical Parameters	Score
Burden of illness: no or mild symptoms	5	Adults (≥18 years) No prior hospital admission for any other reason Absence of acute organ failure (renal, cardiac, respiratory) or decompensation of chronic insufficiency Absence of septic shock and hypotension (systolic pressure <90 mmHg) Absence of severe infections No other serious complications, constituting an admission criterion by themselves (pulmonary thromboembolism, arrhythmias, disseminated intravascular coagulation and bleeding) Solid tumor treated with mild-moderate intensity chemotherapy	Eastern Cooperative Oncology Group performance status (ECOG PS) >= 2	2
No hypotension	5		Stress-induced hyperglycemia (SIH)	2
No chronic obstructive pulmonary disease	4		Chronic obstructive pulmonary disease	1
Solid tumor or no previous fungal infection	4		Chronic cardiovascular disease	1
No dehydration	3		Mucositis National Cancer Institute (NCI) grade >= 2	1
Outpatient status	3		Monocytes < 200 microL	1
Burden of illness: moderate symptoms	3			
Patient's age <60 years	2			

Notes. MASCC, Multinational Association for Supportive Care in Cancer. Points attributed to the "burden of illness" category are not cumulative. The maximal theoretical score is 26. Low-risk patient: score ≥21.
CISNE, the Clinical Index of Stable Febrile Neutropenia. Prognostic categories are defined by the sum of clinical parameters points as low (0 points), intermediate (1–2 points) and high risk (≥ 3 points), with the respective complication rates of 1.1%, 6.2% and 36%.

guidelines, it remains an additional tool which cannot substitute clinical judgment.

Empirical antibiotic therapy

Empirical therapy in low risk patients

Empirical therapy is defined as administration of antibiotic(s) to neutropenic patients with signs or symptoms of infection (Table 1). According to guidelines, a combination of ciprofloxacin and amoxicillin/clavulanate is an appropriate empirical therapy for outpatients who are at low risk of developing complications, provided that FQs have not been used in prophylaxis.[8,128] Additionally, in a double-blind prospective study, the comparison of moxifloxacin vs. the aforementioned regimen showed similar success rates (80% vs. 82%) and overall survival rates (99%) in the 2 arms, although GP BSIs and *P. aeruginosa* infections were more frequent in the moxifloxacin group.[129] In low-risk patients in whom an intravenous treatment is started, the suitable regimens include β-lactams active against *P. aeruginosa*, and a subsequent stepdown to oral therapy can be considered.[97] The feasibility of oral outpatient empirical treatment depends also on the possibility of rapidly reaching the hospital if clinical conditions deteriorate.

Empirical therapy in high risk patients

In high risk patients, such as presenting with severe clinical disease, comorbidities or with expected long duration of neutropenia, hospital admission is advisable. These patients should be treated empirically with an anti-pseudomonal β-lactam, the choice of which is based on the local epidemiology and the individual risk factors for resistant GN rods. Ceftazidime, cefepime, meropenem, imipenem-cilastatin and piperacillin-tazobactam showed similar efficacy, although the latter was associated with a lower mortality in a review of 44 trials.[130] According to a meta-analysis, the addition of aminoglycosides did not improve the outcome while it significantly increased renal failure rates.[131] Therefore, most of the guidelines recommend firmly a β-lactam monotherapy.[8,13,132] Only German experts suggest, with a low level of evidence, the inclusion of an aminoglycoside in the initial empirical therapy in case of severe sepsis or septic shock, based on the results coming from a large retrospective study.[26,133]

In settings with low prevalence of resistance among GN bacteria, there is no benefit of using very broad spectrum agents, such as carbapenems, compared to the aforementioned cephalosporins and piperacillin/tazobactam. However, many centers report nowadays high rates of BSIs caused by ESBL-producing Enterobacteriaceae. Therefore, the choice of the standard empirical β-lactam should take into account the current local prevalence of resistant strains, and carbapenems might be the most suitable options in these settings with a high rate of ESBL-producing bacteria. Additionally, previous infection or colonization with a MDR GN has been associated with a high risk of subsequent infection due to the same pathogen. Therefore, some patients might even need an empirical coverage that is active against carbapenem-resistant Enterobacteriaceae or *P. aeruginosa*. In consideration of the need of initial appropriate coverage of resistant GN bacteria, a de-escalation strategy has been introduced into the management of febrile neutropenia.[13]

Escalation vs. de-escalation strategy

Escalation strategy is characterized by starting an antibiotic which covers most Enterobacteriaceae and *P. aeruginosa*, but not ESBL-producing or MDR strains. Then, if fever persists or if clinical conditions deteriorate, other antibiotics are added and/or the regimen is changed to more broad-spectrum β-lactam, such as a carbapenem.

In contrast, de-escalation approach is defined as upfront administration of a regimen, consisting of either a single drug, such as carbapenem, or a combination of antibiotics, which is active against the most probable resistant bacteria. Then 72–96 hours later, the treatment is re-evaluated and if resistant pathogens are not isolated, it is de-escalated to a simpler or narrower spectrum therapy.

The main advantage of a de-escalation approach is that in the case the infection is caused by a resistant GN strain, there is an initial appropriate coverage provided, even before microbiological data are available, possibly resulting in a reduced mortality. Its main limit is a routine, and frequently unnecessary, use of broad spectrum drugs such as carbapenems, or of a combination therapy with nephrotoxic agents such as aminoglycosides or colistin or vancomycin. This might have important consequences in terms of side effects, cost and excessive antibiotic pressure, particularly in case of failure to de-escalate. On the contrary, escalation strategy minimizes the antibiotic pressure, allowing a subsequent switch or addition of other drugs if a resistant strain is isolated.

The choice of patients who may benefit from a de-escalation approach is particularly challenging. In fact, this strategy has been proposed for febrile neutropenic patients with severe clinical presentation and with previous infection or colonization by MDR bacteria or in centers where resistant bacteria (for example ESBL-producing ones) are frequent.[13]

Until now, there is little data on the applicability and the efficacy of this novel approach to febrile neutropenia. Outside neutropenic population, de-escalation strategy has been successfully used in intensive care units (ICU) for over a decade and several papers have reported a survival benefit or, at least, no detrimental effect on mortality rates.[134-136] The first study which enrolled neutropenic patients reported that de-escalation was performed in 44% of patients within the first 12 days after ICU admission.[137] No standardized rules were established for antibiotic switch, leaving to senior doctors the decision to reduce the β-lactam spectrum or to discontinue drugs active against MRSA. This prospective observational analysis did not show any increase in mortality rate at 30 days and at one year after ICU discharge in the de-escalation group. It is worth noting that in that cohort antibiotic treatment was continued until the resolution of neutropenia in all cases.[137]

Empirical coverage of Gram-positive bacteria

The debate regarding the role of vancomycin in empirical treatment is particularly valid for settings with a high prevalence of resistant GP, such as methicillin-resistant staphylococci. Currently glycopeptides are not recommended for the first line empirical therapy, unless a high suspicion of GP infection (e.g., CVC involvement, skin and soft tissue infections, pneumonia), hemodynamic instability, known MRSA colonization or high prevalence of MRSA are present.[8] This statement is based on several evidences,[138,139] with the latest meta-analysis confirming no benefit on 30-day mortality and on overall treatment failure of the anti-GP coverage.[59] Moreover, despite earlier demonstrations of improved outcome in viridans streptococci BSIs treated with vancomycin,[140] piperacillin-tazobactam, carbapenems and cefepime offer good coverage of VGS strains with MIC lower or equal to 2 μg/mL, making the addition of a glycopeptide unnecessary.[8]

Of note, early de-escalation should also be applied also to combination therapies which include glycopeptides or other antibiotics active against resistant GP, if blood cultures (or BAL in case of pneumonia) do not grow resistant strains.

Daptomycin and linezolid are alternatives to vancomycin in case of infections caused by resistant staphylococci and enterococci. For daptomycin, in neutropenic patients with GP infections a success rate of 85% has been reported.[141] Also in a randomized, double-blinded comparison between vancomycin and linezolid in febrile neutropenic patients with suspected GP infections, clinical and microbiological success rates were similar in both arms, although the white blood count recovery was delayed in the linezolid group.[142] On the contrary, neutrophil engraftment time was found to be similar in a retrospective case-control study on the use of linezolid during neutropenia.[143] The role of novel anti-GP drugs such as cephalosporins with anti-MRSA activity, tedizolid, telavancin, dalbavancin, and oritavancin remains to be established in neutropenic patients.

Other aspects of management of BSIs in neutropenia

As a part of the efficacious treatment, CVCs should be removed when a CVC-associated infection is caused by certain bacteria or fungi, such as *S. aureus, P. aeruginosa*, or *Candida*. NCCN guidelines suggest applying the same approach for *Acinetobacter* spp. and VRE.[5] The CVC removal is also advisable in case of hemodynamic instability, tunnel or port pocket infections, endocarditis,

septic thrombosis and if blood cultures are still positive after ≥ 72 hours of appropriate therapy.[8]

The length of antibiotic treatment in neutropenic patients is another issue that has been recently re-addressed. In particular, in case of patients treated empirically and with no clinically or microbiologically documented infection, who are afebrile for at least 48 hours and who are stable since the onset of the symptoms, discontinuation of antibiotics before the resolution of neutropenia has been proposed.[13] In microbiologically or clinically-documented infections, the treatment should be based on microbiology results or the epidemiological data on the most probable causative bacteria, and continued as suitable for a given species and infection site. Targeted treatment in hematology patients is beyond the scope of this paper and has been recently reviewed.[144]

Therapeutic options for resistant GN bacteria are limited and the best treatment of carbapenem-resistant pathogens is, so far, still unknown. Usually, a 3-drug combination therapy is started, including colistin or gentamycin, high dose carbapenem and tigecycline or fosfomycin.[145-148] Despite testing as resistant, meropenem, administered in high dose and in prolonged infusion, has been associated with a survival benefit in treatment of carbapenem-resistant *K. pneumoniae*, particularly in case of strains with MIC values only few dilutions above the breakpoint for resistance.[146-148] Hopefully, novel molecules, such as recently marketed in the US new β-lactamase inhibitor - avibactam or a new antipseudomonal cephalosporin - ceftolozane, and others would help in treating the MDR GN infections.[149]

Conclusions and future perspective

Clinical management of neutropenic patients is offering new clinical challenges. Nowadays the spread of resistant bacteria across various countries highlights the need for surveillance, better knowledge of local epidemiology and for global infection control. Antimicrobial stewardship programs should be implemented in every cancer center in order to optimize the antibiotic treatments in terms of drug choice, dosage and duration of administration, with the ultimate aim of improving the patients' outcome. Secondary goals are represented by reducing side effects and costs associated with MDR infections and their treatment. The individualized choice of empirical treatment of febrile neutropenia is necessary. The effectiveness of de-escalation strategy needs robust confirmation and should be investigated in large trials involving neutropenic patients. New diagnostic tests are urgently required, especially for rapid detection of MDR strains. Finally, new drugs are expected to provide therapeutic options against MDR or pan-resistant strains.

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
BSIs	Bloodstream Infections
CDC	Centers for Disease Control and Prevention
CLABSI	Central Line-Associated Blood Stream Infections
CLSI	Clinical and Laboratory Standards Institute
CRP	C-Reactive Protei
CVC	Central Venous Catheters;
ECDC	European Center for Disease Prevention and Control
ECIL	European Conference on Infections in Leukemia
ESBL	Extended-Spectrum Beta-Lactamase
EORTC	European Organization for Research and Treatment of Cancer
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FQs	Fluoroquinolones
GN	Gram-negative
GP	Gram-positive
HSCT	Haematopoietic Stem Cell Transplantation;
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
MASCC	Multinational Association for Supportive Care in Cancer
MBI-LCBI	Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection
MIC	Minimal Inhibitory Concentration
MDR	Multidrug Resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
NCCN	National Comprehensive Cancer Network
PCR	Polymerase Chain Reaction
PCT	Procalcitonin
PICC	Peripherally Inserted Central Catheter
SIRS	Systemic Inflammatory Response Syndrome
VGS	Viridans Group Streptococci
VRE	Vancomycin-resistant enterococci

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