Antibacterial Resistance in Patients with Hematopoietic Stem Cell Transplantation

Sehnaz Alp¹ and Murat Akova²

¹ Associate Professor, Hacettepe University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
² Professor, Hacettepe University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey

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Abstract. Recipients of hematopoietic stem cell transplantation (HSCT) are at substantial risk of bacterial, fungal, viral, and parasitic infections depending on the time elapsed since transplantation, presence of graft-versus-host disease (GVHD), and the degree of immunosuppression. Infectious complications in HSCT recipients are associated with high morbidity and mortality. Bacterial infections constitute the major cause of infectious complications, especially in the early post-transplant period. The emergence of antibacterial resistance complicates the management of bacterial infections in this patient group. Multidrug-resistant bacterial infections in this group of patients have attracted considerable interest and may lead to significant morbidity and mortality. Empirical antibacterial therapy in patients with HSCT and febrile neutropenia has a critical role for survival and should be based on local epidemiology. This review attempts to provide an overview of risk factors and epidemiology of emerging resistant bacterial infections and their management in HSCT recipients.

Keywords: Hematopoietic stem cell transplantation, antibacterial resistance, resistant bacterial infection.

Introduction. Hematopoietic stem cell transplantation (HSCT) has become the treatment of choice to cure or improve the outcomes of a wide variety of haematological malignancies and disorders.¹⁻⁴ HSCT can be performed by the transfer of hematopoietic stem cells from the donor to the recipient (allogeneic HSCT) or by the return of previously harvested cells of the same individual (autologous HSCT) after administration of conditioning regimens.⁴ Myeloablative (MA) conditioning leads to profound pancytopenia, and also breaks down mucosal barriers, which might result in seeding of residing microorganisms of the gastrointestinal system into the bloodstream. Therefore, infectious complications begin to appear in the early post-transplant period. Nonmyeloablative (NMA) conditioning has the advantages of reduced regimen-related toxicity and transplant-related mortality. Therefore, patients being referred for HSCT but not eligible to receive a myeloablative conditioning may have the opportunity to benefit from HSCT. Recipients of NMA allogeneic HSCT experience a heterogeneous duration and degree of pancytopenia according to the administered regimen. NMA regimens with lower mucosal toxicity and myelosuppression provide a low incidence of infectious complications within the
early period after transplantation. Immune recovery after NMA regimens was shown to be faster than that was seen following MA regimens, and improved immune reconstitution was associated with lower incidence of life-threatening infectious complications. Even though myelosuppressive potential of NMA regimens seems to be milder than MA regimens, the severity and duration of lymphodepletion is assumed to be similar, because of the implementation of immunosuppressive treatment to prevent graft rejection.\(^4\)

### Risk factors for bacterial and resistant bacterial infections in patients with HSCT.

Infectious complications are the major contributors of morbidity and mortality, especially within one year following HSCT. In the early post-transplant period, presence of neutropenia and mucosal damage predispose patients to infections. Presence and severity of graft-versus-host disease (GVHD) and immunosuppressive treatment for it have a considerable impact on the degree of overall immunosuppression and risk of infection.\(^4,7\) The frequent use of central venous catheters brings about a substantial risk for severe, often recurrent, and potentially lethal infections.\(^9,11\) Recipient factors such as age, comorbidities, and previous exposure to infectious agents prior to transplant, and the type of transplant, due to the distinct duration required for immune reconstitution, also influence the risk of infectious complications.\(^4\)

Initiating broad-spectrum empirical antibacterial therapy results in decreased mortality in febrile neutropenic HSCT recipients. On the other hand, the use of such therapy has the risk of selection of resistant pathogens.\(^9,12-14\) Fluoroquinolone prophylaxis in haematology settings led emerging fluoroquinolone resistance.\(^15-20\) This prophylaxis has also been associated with emerging methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant (MDR) *Escherichia coli*, and *Pseudomonas aeruginosa* bacteriaemia, and *Clostridium difficile* infections.\(^21-25\) Consequently, empirical carbapenem use in patients receiving quinolone prophylaxis has increased, a practice may, in turn, result in increased carbapenem-resistant bacterial infections.\(^16,26\) In addition, prolonged and/or repeated hospitalisations, intensive care unit (ICU) stay, severity of illness, healthcare-associated infections, presence of urinary catheter and older age are considered as major risk factors for resistant bacterial infections.\(^12,26-30\) Main risk factors for certain resistant bacterial infections are summarised in the Table 1.

| Resistant bacteria | Risk factors |
|-------------------|--------------|
| **Methicillin-resistant *Staphylococcus aureus*** | Previous or prolonged hospital stay; exposure to antibiotics (quinolones, glycopeptides, and cephalosporins); older age (≥65 years); surgical intervention within last 4 weeks; open skin lesions; enteral feeding; skin graft-versus-host disease |
| **Vancomycin-resistant *Enterococcus* spp.** | Colonisation with vancomycin-resistant *Enterococcus* spp. on hospital admission; exposure to antibiotics (oral vancomycin, extended-spectrum cephalosporins, and metronidazole); presence of neutropenia more than 7 days; severe mucositis; *Clostridium difficile*-associated diarrhea |
| **Extended-spectrum beta-lactamase-producing Enterobacteriaceae** | Prolonged hospital stay (≥21 days); admission to intensive-care unit; central venous catheter; urinary catheter; severe illness; ventilatory assistance; hemodialysis; emergent abdominal surgery; gastrostomy or jejunostomy; gut colonisation; exposure to broad-spectrum antibiotics; travel to endemic area |
| **Carbapenemase-producing Enterobacteriaceae** | Exposure to antibiotics (carbapenems); older age (≥65 years); prolonged hospital stay (≥21 days); travel and stay in endemic area |
| **Pseudomonas aeruginosa** (Resistant to at least 3 classes of anti-pseudomonal drugs) | Exposure to antibiotics (quinolones, metronidazole, third-generation cephalosporins, carbapenems); acute myeloid leukaemia; endogenous and/or water source |
| **Acinetobacter baumannii** (Resistant to more than 2 of the following drug classes: cephalosporins (antipseudomonal); carbapenems (imipenem or meropenem); penicillin (ampicillin-sulbactam); fluoroquinolones (ciprofloxacin or levofloxacin); aminoglycosides (amikacin, gentamicin, tobramycin) | Intravascular catheters; trauma or burns; chronic lung disease; travel and stay in endemic area |
Antibacterial resistance in patients with HSCT. The data on epidemiology of bacterial infections and their resistance patterns in HSCT recipients mostly reflect isolates from bloodstream infections (BSIs) which are the most frequent microbiologically documented bacterial infections. The rate of BSIs varies between 20-30% of allogeneic and 5% of autologous HSCT recipients, especially within pre-engraftment phase. Even though bacterial pneumonia and skin and soft tissue infections are also common among these patients, microbial aetiology may remain undocumented.29,31

During 1960s and 1970s, the incidence of gram-negative infections was high in haematology settings. Nevertheless, the incidence of gram-positive pathogens increased during mid-1980s and 1990s as a result of extensive use of indwelling catheters, early-generation fluoroquinolone prophylaxis and broad-spectrum empirical anti-gram-negative antibacterial therapy.12,29,32-34 Afterwards, coagulase-negative staphylococci were reported as the most common bacterial etiologic agents isolated from blood cultures in most centres.10,35 However, recent reports from a number of centres revealed drug-resistant gram-negative pathogens such as ESBL-producing gram-negative bacteria, multidrug resistant (MDR) P. aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, and carbapenemase-producing gram-negative bacteria as the causative agents of increasing numbers of infections.9,12,36-44 In countries where high rates of antibiotic resistance exist, ESBL-producing or MDR gram-negative bacteria contribute up to 13-14% of clinical isolates.26,28,40,45 A significant increase in the prevalence of resistant gram-positive cocci such as MRSA and vancomycin-resistant enterococci (VRE) have also been reported and stated as the overriding resistant pathogens in some centres.46,47 Penicillin-resistant viridans streptococci and penicillin-resistant Streptococcus pneumoniae (PRSP) are less common, yet they may be the causative agents of severe infections.9,10,12,48

The epidemiology of bacterial infections and their resistance patterns show distinct geographic and inter-centre variability. Being aware of the current data on local epidemiology of predominant pathogens and close monitoring of their resistance patterns are of great importance, especially in empirical antibacterial treatment decisions.12,25,49,50 Recent reviews on epidemiology of BSIs in cancer patients, primarily with hematologic malignancies including HSCT recipients, revealed that among all BSI isolates, coagulase-negative staphylococci and Enterobacteriaceae (frequently E. coli) were the most common pathogens followed by P. aeruginosa, S. aureus, viridans streptococci, and enterococci. The approximate rates of these commonly encountered pathogens were: 25% (range: 5-60%) for coagulase-negative staphylococci; 25% (range: 6-54%) for Enterobacteriaceae; 10% (range: 0-30%) for P. aeruginosa; 6% (range: 0-20%) for S. aureus; 5% (range: 0-16%) for viridans streptococci; and 5% (range: 0-38%) for enterococci.29,49,51

A brief information on the epidemiology of global resistance data for gram-positive and gram-negative bacteria is given below in each corresponding title. An online website showing the current drug resistance rates and antimicrobial use worldwide is also available at ‘http://resistancemap.cdc.gov’.

Gram-Negative Bacteria. E. coli is one of the most frequent pathogens causing bacteraemia in patients with cancer and neutropenia.39,51-53 Production of one or more extended spectrum beta-lactamases (ESBLs) is the main resistance mechanism against broad-spectrum penicillins and cephalosporins in enteric gram-negative pathogens. Many ESBL-producing E. coli are also resistant to non-beta-lactam antibiotics including aminoglycosides and quinolones with altered resistance mechanisms.52-54 ESBL-encoding plasmids may also encode resistance to aminoglycosides, tetracyclines, sulphonamides and trimethoprim.52,55 These plasmids frequently encode an inhibitor-resistant beta-lactamase, which confers resistance to beta-lactam-beta-lactamase inhibitor combinations including amoxicillin-clavulanate and piperacillin-tazobactam.52,55,56 Aminoglycoside resistance among E. coli and other gram-negative enteric pathogens is determined by aminoglycoside-modifying enzymes which can be encoded on the same plasmid with ESBLs.52 E. coli was the second most frequent carbapenem-resistant Enterobacteriaceae (CRE) following Klebsiella pneumoniae. In a recent US survey, the incidence of CRE was determined as 2.93 per 100,000 population.52,57
One of the most significant carbapenemases described in Enterobacteriaceae is New Delhi metallo-beta-lactamase-1 (NDM-1). This enzyme is prevalent in the Indian subcontinent, but also frequently reported in Balkans and the Middle East.\textsuperscript{52,58} The bacteria harbouring this enzyme have spread worldwide and are usually only susceptible to colistin, tigecycline and fosfomycin, although susceptibility to these agents is not universal.\textsuperscript{52,59} Since \textit{E. coli} infections are very frequent in the outpatient settings, it is feared that a progressive increase in the prevalence of NDM-1 producing \textit{E. coli} may occur.\textsuperscript{52,58} Plasmid-mediated colistin resistance (via \textit{mer-1} colistin resistance gene) has recently been described in \textit{E. coli} isolates worldwide from mainly livestock and less frequently in human samples.\textsuperscript{52,60-65} The implications of this finding may be horrendous since the offending plasmid can easily be transferred between \textit{E. coli} strains and to \textit{K. pneumonia} and \textit{P. aeruginosa}.\textsuperscript{52,66} As a matter of fact, recent reports already noted the presence of this gene from plasmids in \textit{Salmonella} and \textit{K. pneumoniae}.\textsuperscript{52,67-70}

Along with ESBLs as the main resistance mechanism to broad-spectrum penicillins and cephalosporins in enteric gram-negative pathogens, carbapenem resistance has become the most important epidemiologic and therapeutic challenge in \textit{K. pneumoniae}.\textsuperscript{52,58} There are mainly 3 classes of carbapenemases involved including KPC (Class A), OXA-48 (Class D) and NDM (Class B) for which different epidemiological reservoirs exist.\textsuperscript{52,58,59,71-74} A specific KPC-2 or KPC-3-producing clone has been widely disseminated worldwide contributing the spread of resistance.\textsuperscript{52,58} Carbapenem-resistant isolates usually show MDR pattern and are susceptible only to colistin, fosfomycin and tigecycline. However, there is also emergence of resistance against these antibiotics.\textsuperscript{52,75,76}

\textit{P. aeruginosa} strains with high resistance rates to aminoglycosides, ceftazidime, quinolones, piperacillin-tazobactam and carbapenems are usually reported from Southern and Eastern part of Europe.\textsuperscript{52,77} Several beta-lactamases have been described for causing resistance and these include AmpC, ESBL (particularly PER-1) and metallo-beta-lactamases.\textsuperscript{52,55} Carbapenem resistance in \textit{P. aeruginosa} is mostly due to porin deficiencies and rarely caused by carbapenemase production.\textsuperscript{52,78} Emergence of colistin resistance in \textit{P. aeruginosa} has also been reported.\textsuperscript{52,79}

The most frequent Class A ESBLs found in \textit{A. baumannii} are PER-, GES- and VEB-type enzymes. These beta-lactamases confer resistance to extended-spectrum cephalosporins, but inhibited by tazobactam and clavulanic acid.\textsuperscript{52,78} TEM-, SHV- and CTX-M-type ESBLs are rarely found in \textit{A. baumannii}. Class B beta-lactamases (metalloenzymes) are also reported in \textit{A. baumannii} and include IMP-, VIM- and NDM-type enzymes. These beta-lactamases provide activity against not only to carbapenems, but also to broad-spectrum cephalosporins and penicillins. Class D, OXA-type carbapenemases are the most widespread carbapenemases in \textit{A. baumannii}.\textsuperscript{52,55} These enzymes cause weak resistance to carbapenems. Thus, high-level resistance usually require other mechanisms involved such as efflux and porin loss.\textsuperscript{52,78} The ArmA enzyme is the most frequent methylase which is responsible for high-level resistance to all aminoglycosides in \textit{A. baumannii}. The gene responsible for this enzyme is often identified among OXA-23-producing \textit{A. baumannii} strains. Other methylases are also described.\textsuperscript{52,78} Overexpression of efflux pumps can provide resistance to quinolones. These pumps also use aminoglycosides, tetracyclines, chloramphenicol and trimethoprim as substrates. Thus, quinolone resistance can be selected by non-quinolone antibiotics as well. Usually several of these mechanisms are present in MDR \textit{Acinetobacter} isolates.\textsuperscript{52}

For treatment of MDR gram-negative infections, especially due to carbapenem-resistant Enterobacteriaceae, \textit{Pseudomonas} species, and \textit{Acinetobacter} species, colistin (polymyxin E) has been increasingly used as a therapeutic option, administered as monotherapy or in combination regimens, even though limited data exist on its use in haematology patients and HSCT recipients.\textsuperscript{26,28,81,82} There are many reports on successful combination regimens for MDR gram-negative infections.\textsuperscript{26,83-85} Colistin plus rifampicin treatment has shown in vitro and in vivo synergistic activity for \textit{A. baumannii} infections.\textsuperscript{86,87} However, in a multicentre, randomized clinical trial, colistin plus rifampicin revealed no difference in infection-related mortality and length of hospital stay in the treatment of serious infections due to extensively
drug-resistant *A. baumannii* as compared to colistin alone, but a significant increase in microbiological eradication rate was determined in the colistin plus rifampicin arm.\(^8\) In a recent study, survival benefit with combination therapy (colistin plus carbapenem or tigecycline plus carbapenem) was demonstrated in patients with KPC-producing *K. pneumoniae* bacteraemia.\(^8\)

**Gram-Positive Bacteria.** Methicillin resistance is the hallmark of antimicrobial resistance in *S. aureus* and coagulase-negative staphylococci.\(^52\) While, vancomycin has long been successfully used for treatment of MRSA infections, emergence of *S. aureus* strains with vancomycin MICs \(\geq 2\) mg/L has coincided with reports of treatment failures.\(^9,90\) Community-acquired MRSA (CA-MRSA) infections have emerged as a global problem since the beginning of the 21\(^{st}\) century.\(^51,90-92\) Although CA-MRSA strains initially caused mainly skin and soft tissue infections in healthy individuals and some certain populations such as homeless and imprisoned people, increased rates of bacteraemia both in community and hospital setting; ventilator associated pneumonia; and surgical site infections have recently been reported.\(^52,94,95\) CA-MRSA isolates usually remain susceptible to many non-beta-lactam antibiotics including clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX).\(^52,96\)

Coagulase-negative staphylococci are the most common cause of nosocomial BSIs and are responsible almost one-third of all healthcare-associated bacteraemia. The incidence is highest in those with cancer and neutropenia and those with catheter- and/or prosthetic device-related infections.\(^29,52,97\) Multiple antibiotic resistance is highly encountered among hospital isolates and usually related with methicillin resistance.\(^52,98\) Resistance to vancomycin is very rare, however a 20.8% resistance to teicoplanin was reported from UK, particularly in *S. haemolyticus*.\(^98\)

Penicillin-resistant pneumococci are more likely to show higher resistance to other classes of antimicrobials. Current figures of resistance in the US include 35% to macrolides, 10% to clindamycin, 30% to TMP-SMX, 18% to doxycycline and 2% to respiratory quinolones.\(^52,99\) Higher rates of macrolide resistance are reported from Europe.\(^52,100\)

Viridans streptococci can cause infective endocarditis, especially in patients with compromised heart valves, and they can also produce bacteraemia and septic shock particularly in patients with neutropenia.\(^51,52,101\) Although these bacteria are susceptible to most antimicrobials, beta-lactam resistance, due to the altered penicillin binding proteins has emerged and may cause a significant problem especially in patients with immunosuppression and bacteraemia.\(^51,52,102\)

Ceftriaxone and cefepime resistance has been reported up to 23 and 25%, respectively in strains isolated from hospitalised or cancer patients.\(^52,103,104\) Vancomycin is highly effective on such strains.\(^52\)

Among all enterococci, *Enterococcus faecium* is the most challenging one in terms of antibacterial resistance and therapy. In the US, enterococci are the second most common bacteria isolated from catheter-related (CR)-BSIs.\(^52,105\) Enterococci are intrinsically resistant to many antimicrobials, but also easily acquire mutations and exogenous genes to develop further resistance.\(^52,106\) While aminopenicillin resistance is rare in *E. faecalis*, it is encountered around 90% of nosocomial *E. faecium* isolates.\(^52,100,106\) Beta-lactamase production is infrequently associated with resistance and can be overcome with the use of beta-lactamase inhibitor compounds. The production of PBPs with low affinity to penicillins is the major culprit for beta-lactam resistance.\(^52,106\) High-level resistance to all aminoglycosides eliminates the synergistic activity of penicillins and vancomycin both of which can enhance activity of aminoglycosides in enterococci with low-to-moderate resistance. High-level aminoglycoside resistance has increased in both *E. faecalis* and *E. faecium* during the last 3 decades.\(^52,100\) Glycopeptide resistance in enterococci is a much bigger problem in the US than in Europe and elsewhere. By 2007, >80% of *E. faecium* isolates in the US hospitals were reported to be resistant to vancomycin whereas in Europe only Ireland reported a resistance rate of >50%.\(^52,100,106,107\) Similarly, MDR enterococci is much more prevalent in the US.\(^52,106\) Enterococci are the third most frequent agents of bacteraemia in haematological cancer patients and HSCT recipients and may affect up to 12% of all transplant patients. On these patient groups, a shift from *E. faecalis* to *E. faecium* has resulted in higher rates of VRE infections.\(^51,52\) However, similar to the general epidemiology, VRE infections constitute a less significant problem in
Western European transplant centres with <5% of enterococci being resistant to vancomycin.\textsuperscript{52,104} Resistance to linezolid and daptomycin is rarely reported.\textsuperscript{52,108}

Newer agents with activity against glycopeptide non-susceptible gram-positive pathogens, such as daptomycin, linezolid, and tigecycline are being increasingly used in various clinical settings.\textsuperscript{9,12,27,29,109} One of the major drawbacks of daptomycin is the inactivation of the drug by pulmonary surfactant, which limits its use in treatment of pneumonia. Moreover, treatment failure in staphylococcal central nervous system infection was noticed.\textsuperscript{26,110} Even though daptomycin had not been evaluated in controlled trials in haematology patients, its efficacy on gram-positive infections in neutropenic patients has been reported.\textsuperscript{26,111,112} The clinical utility of tigecycline is limited by its low peak-serum concentrations, and increased failure and mortality rates.\textsuperscript{26,113,114}

\textit{C. difficile} infection (CDI) is among the major concerns in patients undergoing HSCT. Risk factors for CDI in HSCT patients are specified as exposure to broad-spectrum antimicrobial agents, receipt of chemotherapy prior to conditioning for HSCT, total body irradiation, presence of acute GVHD, and VRE colonisation.\textsuperscript{115–118} The outcomes of CDI include increased morbidity and mortality due to increased risk of developing complications such as colitis or toxic megacolon, extended hospital stays, necessity to discontinue the required antibiotics, and increased healthcare costs.\textsuperscript{119,120} The emergence of an epidemic strain termed as ‘North American PFGE type 1 or NAP1’ is associated with large outbreaks in Europe and the United States. NAP1 has a genetic alteration that results in enhanced toxin production and has been associated with increased severity of CDI, higher relapse and mortality rates.\textsuperscript{9,121,122}

Even though the studies conducted in 1980s and 1990s revealed that orally administered metronidazole and vancomycin showed equal effectiveness for treatment of CDI\textsuperscript{9,123,124} with the emergence of the epidemic strain, reports of higher rates of treatment failure or delayed treatment responses have appeared with metronidazole as compared to oral vancomycin.\textsuperscript{125–128} There are variable data on the outcomes of CDI in haematology settings, but treatment response to metronidazole and vancomycin is reported to be similar.\textsuperscript{26,129–131} While initiation of treatment for CDI, age, white blood cell count, and serum creatinine level should be taken into consideration as indicators for severe or complicated course.\textsuperscript{122,132} For the initial episode of mild-to-moderate CDI, metronidazole is the drug of choice. Vancomycin should be preferred for an initial episode of severe CDI. In case of existence of ileus, megacolon, hypotension or shock, vancomycin at higher doses (500 mg 4 times per day) plus metronidazole can be administered. In recurrent CDI, the recommendations for first recurrence are the same as for initial episode. However, in second recurrence, vancomycin (in a tapered and/or pulsed regimen) is the drug of choice.\textsuperscript{132}

The data on alternative treatment options for CDI are limited in haematology patients and HSCT recipients. With the use of fidaxomicin, clinical response and recurrence rates were found to be comparable to that of conventional therapy.\textsuperscript{133} However, fidaxomicin was associated with a lower recurrence rate of CDI associated with NAP1 strains.\textsuperscript{134} In a recent post hoc analysis, fidaxomicin was found to be superior to vancomycin for treatment of CDI in patients with cancer in terms of shorter time to resolution of diarrhoea, higher cure and sustained response rates, and fewer recurrences.\textsuperscript{135}

\textbf{Screening of MDR Bacteria in Patients with HSCT.} Infection prevention and control measures such as hand hygiene, contact barrier precautions, isolation, and appropriate environmental cleaning are crucial to deal with the spread of MDR bacteria in haematology settings.\textsuperscript{144,146} Active surveillance can help to identify individuals colonised with MDR pathogens. However, it is not clearly defined whether an active-surveillance for MDR bacteria as an additional strategy to infection control procedures is beneficial to prevent health-care-associated transmission.\textsuperscript{144,147–149} Colonisation may persist for months in the case of severe underlying disorders, prolonged or recurrent antimicrobial exposure, and presence of invasive devices.\textsuperscript{144,150} Patient populations for targeted screening, as well as ideal screening method and timing of surveillance, are not definitely determined, but can be chosen among those considered to have risk factors for colonization with MDR pathogens, such as prolonged hospital stay, exposure to antimicrobials, ICU stay or transfer from settings known to have high MDR bacteria rates. Another
approach is to obtain surveillance cultures from each patient admitted to the settings with high prevalence of MDR pathogens. While some centres establish weekly surveillance cultures, others choose to obtain cultures at the time of admission and/or whenever risk factors emerge for colonisation of MDR bacteria.\(^\text{[144,150-153]}\)

Screening for MRSA colonisation is not routinely performed, but can be established if MRSA rates remain to be high despite effective implementation of infection control measures. In such circumstances, MRSA surveillance cultures should be obtained on admission and thereafter (e.g. weekly) with or without concomitant decolonization.\(^\text{[144,154-156]}\) VRE surveillance cultures can be considered in case of ongoing spread of VRE in an HSCT unit to identify colonised patients.\(^\text{[144,152]}\)

Active surveillance cultures for MDR-GNBs can be used in units with high rates of MDR-GNB infections. A point prevalence survey is recommended if previously unnoticed cases with CRE are identified by the review of microbiology reports for the preceding 6-12 months.\(^\text{[144,146]}\) In a retrospective nationwide survey from Italy, documented carbapenem-resistant \textit{K. pneumoniae} (CRKp) colonization before or after HSCT was determined to be followed by infection in 25.8% of autologous HSCT and 39.2% of allogeneic HSCT recipients; and infection-related mortality rates were stated as 16% in autologous HSCT and 64.4% in allogeneic HSCT patients.\(^\text{[44]}\) In endemic settings, screening for CRKp before transplantation prior to hospital admission and weekly after transplantation for those who remain negative in case of isolation of CRKp in that unit is recommended.\(^\text{[157,158]}\) Recent reports have revealed that decolonization with aminoglycosides or colistin could succeed in patients colonised with CRE.\(^\text{[157,159-163]}\) Nevertheless, development of resistance to these agents is of concern, and patients can be colonized after gastrointestinal decolonization.\(^\text{[158,159,164-167]}\)

Management of Febrile Neutropenia in the Era of Resistant Bacterial Infections. For empirical antibacterial treatment in febrile neutropenia, escalation or de-escalation approach can be used. In escalation strategy, initial therapy targets activity against Enterobacteriaceae and \textit{P. aeruginosa}, but, ESBL- and carbapenemase-producing gram-negative bacilli and drug-resistant non-fermentative bacteria remain out of empirical coverage. In case of development of clinical deterioration or isolation of a resistant pathogen from clinical samples, the spectrum of antibacterial coverage must be broadened. In de-escalation strategy, initial regimen targets to cover drug-resistant pathogens, and once the microbiological data become available, therapy is de-escalated to an appropriate narrower spectrum. Escalation strategy may be considered for patients followed in a centre where MDR pathogens are rarely seen at the onset of febrile neutropenia and for those without any specific risk factors for resistant bacterial infections. De-escalation strategy may be used for febrile neutropenic patients having risk factors for resistant bacterial infections, such as previous infection or known colonisation with ESBL-producing gram-negative bacteria, residents of a centre where MDR pathogens are common, and also for those presenting with septic shock and pneumonia. Initial regimen in de-escalation strategy may include monotherapy with a carbapenem or combination therapy with an anti-pseudomonal beta-lactam agent and an aminoglycoside/quinolone or combination therapy with colistin and a beta-lactam agent/rifampicin. If risk factors for resistant gram-positive infections are present, early coverage with a glycopeptide or newer agents (linezolid, daptomycin, tigecycline) with activity against glycopeptide non-susceptible gram-positive pathogens should be considered. Patients with suspicion of catheter-related infection, known colonisation with MRSA, VRE, and PRSP, hemodynamic instability, severe sepsis, septic shock, presence of skin and soft tissue infection and pneumonia are accepted as candidates for additional antibiotics against resistant gram-positive pathogens.\(^\text{[12,27-29,51]}\)

\textbf{Conclusion.} The emergence of infections with resistant bacterial pathogens is associated with trends towards poor outcomes, prolonged hospital stay, more frequent ICU admissions, and increased treatment costs in haematology patients.\(^\text{[26,45,136-138]}\) Moreover, the bacterial resistance complicates the use of standard antimicrobial regimens in febrile HSCT recipients. Antimicrobial treatment approach for neutropenic or chronically immuno-suppressed HSCT recipients with GVHD necessitates careful evaluation of patients; detailed knowledge on local epidemiological data on
antibacterial resistance; close monitoring of the emergence of resistance in bacterial pathogens; and use of robust treatment options in the context of a rational antimicrobial stewardship program. 

Convenient infection control measures and appropriate vaccination schedules should be implemented to prevent patients from exposure to pathogens. Besides, effective attempts should be provided in the development of new antibacterial agents and immune augmentation strategies to cope with resistant bacterial pathogens.

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