Trakia Journal of Sciences, No 3, pp 266-278, 2023

Available online at:
http://www.uni-sz.bg

ISSN 1313-3551 (online) **doi:10.15547/tjs.2023.03.008**

Review

INFECTIOUS COMPLICATIONS, ASSOCIATED WITH MULTI-DRUG RESISTANT BACTERIA IN PATIENTS FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION – RESISTANCE MECHANISMS AND THERAPEUTIC OPTIONS

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ABSTRACT
Individuals undergoing hematopoietic stem cell transplantation are a peculiar group of patients in whom the risk of developing infectious complications is very high. Various groups of antimicrobials are used for prophylaxis and therapy, but the growing resistance among bacterial isolates is about to derail all attempts to prevent severe infectious complications. The aim of this review is to briefly present the different types of multidrug-resistant bacteria causing infections in these patients, as well as to introduce the most common resistance mechanisms and treatment options for this type of infections.

Key words: stem cell transplantation, infection, bacteria, resistance mechanisms, therapy

INTRODUCTION

In the last decade, there has been a dramatic increase worldwide on the proportion of bacteria, exhibiting multipledrug-resistance (MDR). MDR bacteria are those microorganisms that show resistance to one or more antibacterial agents from at least three different classes of antimicrobials (1). In various studies, over the years, an increase in the frequency of these microorganisms has been documented from < 10% in 1998 - 2000 to over 23% for 2010 - 2011 (2). More recent data indicate that the global incidence of MDR infections is about 36% (3). Some countries are more affected than others - > 70% MDR bacteria in India, while in the USA it is below 20% (3). Due to a number of conditions and risk factors (underlying disease, neutropenia, inserted central venous catheter, prolonged hospitalization, mucositis, and etc.), patients after hematopoietic stem cell transplantation (HSCT) are at risk of developing infectious complications. According to literature data, bacterial complications in this population reach 34% (4), and the cumulative incidence of MDR bacterial infections is about 10.5% (5).

Microorganisms from the family *Enterobacteriacae* (mainly *Klebsiella pneumoniae*), *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the most common causes of MDR infections in the medical practice. Because of their resistance to commonly used antibiotic agents in empiric therapy, MDR bacteria are associated with delays in adequate therapy, leading to a significant increase in morbidity and mortality (6). In addition, the spread of these resistant strains leads to a vicious circle involving the use of broad-spectrum antibiotics, selective pressure and the increase of resistant bacteria (7).

The occurrence of MDR bacterial strains is also associated with individual and epidemiological risk factors: prolonged stay in the hospital, admission to intensive care units, use of broad-spectrum antibiotics for a long period of time, presence of foreign bodies (catheters), oncological and hematological diseases, transplantation, and etc. (1)

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Of greatest importance for medical practice and in particular in the field of hematological malignant diseases are bacteria, producing extended-spectrum beta-lactamases (ESBL), carbapenem-nonsusceptible and colistin-resistant bacteria, as well as vancomycin-resistant enterococci (VRE). In 2017, the World Health Organization (WHO) published a list of MDR bacteria with global priority in order to develop and introduce new antibiotics against these pathogens. Gram-negative bacteria, with multiple resistances, are declared a threat to public health and are included in the group of microorganisms with the highest priority (8).

The aim of this review is to present the most frequent MDR pathogens, causing infections in patients after HSCT, their mechanisms of resistance, as well as the options for therapy.

BACTERIA PRODUCING EXTENDED-SPECTRUM BETA-LACTAMASES (ESBLs)

The most common mechanism of resistance demonstrated in MDR bacteria is the innate or acquired resistance profile by the production of enzymes called beta-lactamases (1). Beta-lactamases are hydrolyzing enzymes that have the ability to destroy the beta-lactam ring, resulting in the inactivation of the various subfamilies of beta-lactam antibiotics. Resistance due to these enzymes can be chromosomal (congenital) or plasmid-mediated (acquired) (9, 10). Depending on their structure and functional groups, beta-lactamases are classified into classes (according to Ambler) and groups (according to Bush-Jacoby-Medeiros). In recent years, there has been an increase in the percentage of Gram-negative bacteria isolated from blood cultures showing resistance to third-generation broad-spectrum cephalosporins (ceftriaxone, cefotaxime, ceftazidime). According to the European Antimicrobial Resistance Surveillance Network (EARS Net) for 2019 in Bulgaria, the share of resistant *Escherichia coli*, *K. pneumoniae* and *P. aeruginosa* isolates to third generation cephalosporins is 38.6%, 75.7% and 30.08%, respectively. The resistance of the same bacterial species in Europe was 15.1%, 31.3% and 14.3%, respectively (11).

Class A includes the enzyme families TEM, SHV, CTX-M, etc. They contain serine at their active site and are not inhibited by EDTA. Representatives of some families (TEM-1, 2 and SHV-1, 11) of this class exhibit a narrow spectrum and hydrolyze only penicillins and cephalosporins from the 1st and 2nd generation, having sensitivity to beta-lactamase inhibitors clavulanic acid, tazobactam and sulbactam. Another part of the enzymes exhibits a wider spectrum and hydrolyze broad-spectrum 3rd and 4th-generation cephalosporins and monobactams and are referred to as ESBLs (12, 13). The genes for these enzymes are widely distributed worldwide and are found in almost all regions in Europe, the USA and Asia (14).

To **class C** beta-lactamases belong the AmpC enzymes. They have cephalosporinase activity and hydrolyze mainly cephalosporins up to the 3rd generation and some cefamycins (cefoxitin), retaining their susceptibility to the 4th generation cephalosporins (15). In some representatives of the order *Enterobacterales* (*K. pneumoniae, E. coli, Proteus mirabilis*), class C enzymes can be found in plasmids and transferred to other Gram-negative bacteria. Such are CMY, ACC, DHA and FOX enzymes. Another part is chromosomally encoded and is found in *Enterobacter* spp., *Citrobacter* spp., *Morganella morganii*, *Hafnia alvei*, etc. (16). AmpC enzymes are not affected by clavulanic acid and EDTA, but are inhibited by cloxacillin and boronic acid (15). The chromosomally encoded AmpC enzymes can be inducible or their production can be constitutive. Strong inducers are clavulanic acid and cephalosporins up to the 3rd generation. After induction, the microorganisms demonstrate a lack of susceptibility to 3rd generation cephalosporins (16). For the first time in Bulgaria, a variant of the DHA enzyme (DHA-1) in the *Enterobacter cloacae* complex was documented in 2016 by Dimitrova et al. (17).

Drugs of first choice for the treatment of infections caused by ESBL-producing microorganisms are carbapenem antibiotics (imipenem, meropenem, ertapenem) (7). In recent years, the growing threat of carbapenem-resistant enterobacteria (CRE) leads to changes in this strategy. Many authors recommend the use of the combination beta-lactam antibiotic/beta-lactamase inhibitor (piperacillin-tazobactam), as an alternative to carbapenems (18). In recent studies on the in vitro effect of this combination against ESBL-producing enteric bacteria, causative agents of bloodstream infections, it is proven that these drugs are not inferior in effectiveness to carbapenems, regardless of the source of infection and the type of causative agent, if they are used in appropriate therapeutic doses (19). Therefore, in stable patients, it is recommended

to start high-dose, with an initial loading dose, therapy with beta-lactam antibiotic/beta-lactamase inhibitor (7, 20). As an alternative to carbapenems, combinations of cephalosporin with beta-lactamase inhibitors can also be used. Ceftazidime-avibactam and ceftolozane-tazobactam are novel agents that demonstrate high activity against ESBL-producing bacteria (21).

CARBAPENEM-RESISTANT (CPR) BACTERIA

The emergence of resistance to carbapenem antibiotics in medically important Gram-negative bacteria (*Enterobacteriaceae*, *Pseudomonas* spp. and *Acinetobacter* spp.) over the past decade leads to the emergence of a serious medical problem, due to the rapid spread of these microorganisms and the lack of new antimicrobial agents with activity against them (22). The most common mechanism for the occurrence of this resistance is the enzymatic one. Carbapenemases are enzymes that can hydrolyze almost all beta-lactam antibiotics, being dominantly identified in bacteria of the family *Enterobacteriaceae*, *Pseudomonas* spp. and *Acinetobacter* spp. (23). In 2019 EARS Net survey established the following partitions for CPR invasive *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* isolates in the European Union: 0.3%, 7.9%, 16.5% and 32.6%, respectively. A negative trend is the evidence of a higher relative share compared to the European one for CPR *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* in Bulgaria according to the same study: 27%, 25.2% and 72%, respectively (24). Carbapenemases are divided into two groups, depending on the structure of their active center:

- Serine-containing - Ambler class A and class D
- Containing zinc - class B

Class A includes the enzymes IMI/NMC, SME, KPC and GES, all of which are associated with a different degree of resistance to carbapenems - from reduced sensitivity to a high resistance level. SME, NMC and IMI enzymes are usually chromosomally encoded, while KPC and GES are found in plasmids. SME enzymes are mainly found in *Serratia marcescens*, while IMI and NMC are sporadically distributed in *E. cloacae* (25). Genes for KPC synthesis are found in plasmids, this is why they are widely distributed among Gram-negative bacteria (mainly *K. pneumoniae*) (23). KPC-producing isolates have been detected in the USA, South America and China. In Europe, KPC producers are most commonly found in the Mediterranean, with Greece and Italy considered endemic areas (26, 27). The most common type is KPC-2. In 1996, the first isolates producing this type of KPC were documented in the USA (28). The GES genes encoding the GES carbapenemase are found in integrons in *K. pneumoniae* and *P. aeruginosa* isolates (25).

The enzymes IMP, VIM, GIM, SIM and NDM are included in **class B** (metallo-beta-lactamases, MBLs). A typical characteristic of these MBL genes is that they are found in plasmids in *Enterobacteriaceae* and sometimes in *P. aeruginosa* and *A. baumannii*. Class B enzymes have been found relatively recently. For the first time in 1980, MBLs were distinguished from the serine-containing carbapenemases and categorized into their own class by Ambler. Later, in 1989, Bush separated these enzymes into a functional group (group 3) (29). MBLs are most commonly found in Europe and the Far East (29). The IMP carbapenemase genes were discovered in 1991 in clinical isolates *S. marcescens* in Japan (30). In 1997, in Verona, Italy, the gene for VIM-1 was discovered in *P. aeruginosa* from clinical material (31). The genes responsible for NDM carbapenemases were first described in 2008 in *K. pneumoniae* from the urogenital system of a patient from New Delhi (32). Since then, isolates carrying NDM-1 have spread throughout the world, with India, Pakistan and Bangladesh being the most affected, and it is currently the most common MBL carbapenemase in *Enterobacteriaceae* and *A. baumannii* (22, 33). In Bulgaria, for the first time in 2016, an NDM-1 producing isolate was documented in *K. pneumoniae* from clinical material by Todorova et al., and later in 2017 also in *Enterobacter asburiae* (34, 35). Class B carbapenemases are one of the most problematic enzymes associated with the emergence of resistant bacteria. This fact originates from their broad spectrum and the absence of antimicrobial agents with an inhibiting effect.

Class D beta-lactamases are enzymes with different activity profiles. They are also known as OXA beta-lactamases, because of their oxacillin-hydrolyzing properties. Some have a relatively narrow spectrum, others exhibit a wider spectrum of action and hydrolyze penicillins and cephalosporins, while OXA-48 and OXA-48-like enzymes possess the

properties of carbapenemases (36). OXA-48-producing isolates are distributed worldwide. Hospital outbreaks have been reported in Germany, France and Spain. Outside Europe, they are often found in isolates from the Middle East and Africa (37). Genes for class D enzymes are found on both chromosomes and plasmids. OXA-23, 24/40 and 58 are mainly found in *A. baumannii* and are characterized by carbapenemases, and OXA-48 dominates in *K. pneumoniae* (25). Typical for OXA-48-like is the weak hydrolysis of carbapenems and broad-spectrum cephalosporins and inhibition of their activity by clavulanic acid and EDTA (38). In Bulgaria, the first cases of bacterial isolates *A. baumannii*, carriers of the genes for OXA-23 and OXA-58 have been documented by Stoeva et al. in 2008 and 2009 (39, 40).

Treatment options for infections caused by CPR Gram-negative bacteria are highly limited, not only because of the lack of susceptibility to all beta-lactam antimicrobials but also because of the multiple resistance they usually demonstrate (resistance to aminoglycosides, fluoroquinolones and sulfonamides) (41).

Nowadays, the antibiotics that are accepted as the means of the last choice for treatment in cases of infections caused by CPR bacteria are: **Polymyxins, represented by colistin,** are antimicrobial agents which systemic use was abandoned in the 1960s - 1970s, due to toxic effects, but with the spread of MDR strains, they returned as last option drugs (42). WHO defines colistin as an antibiotic of critical importance to human medicine. The drug, also known as polymyxin E, is an antibiotic that is produced by Gram-positive microorganisms known as *Paenibacillus polymyxa* (43). It has a fast bactericidal effect, a narrow spectrum of action, affecting a large number of Gram-negative bacteria - *E. coli, K. pneumoniae, P. aeruginosa, A. baumannii,* etc. Unfortunately, colistin resistance develops quickly, including during the ongoing therapy. It is believed that monotherapy is less effective, and associated with higher mortality rates and rapid development of resistance. Conducted studies prove that in order to prevent the development of resistance to colistin, it is recommended to use the agent only in combination with other antimicrobials. Good results have been obtained when combining colistin with rifampicin and with a macrolide in infection with MDR *K. pneumoniae*, a carrier of the *mcr*-1 gene (44). Other successful combinations are colistin + tigecycline; colistin + two carbapenems (ertapenem, meropenem); colistin + rifampin + tigecycline + colistin in inhalation form in cases of ventilator-associated pneumonia (45, 46). Combination therapy has been found to be associated with significantly lower in-hospital mortality and is preferred in high-risk patients. In addition, the benefits of inhalation therapy are associated with reaching a concentration of colistin up to 100x higher than the minimum inhibitory concentration (MIC) of the drug, the possibility to prevent the emergence of resistance and more often successful eradication of the pathogen (47).

Tigecycline is another antibacterial agent that is broad-spectrum and exhibits in vitro activity against many Gram-negative and Gram-positive MDR bacteria, except for *P. aeruginosa*, *Proteus spp.*, *Providencia spp*. and *Morganella morganii* (48-50). Studies have demonstrated comparable effectiveness of tigecycline with other commonly used antibiotics for MDR infections. The best results were obtained in the treatment of soft tissue and complicated intra-abdominal infections (51). A disadvantage of this preparation is its bacteriostatic nature and the low serum levels that are reached after its administration (52; 53; 55). The standard antibiotic dosage is 100 mg every 12 hours as a loading dose and 50 mg every 12 hours thereafter (51).

The **carbapenems** imipenem, meropenem and ertapenem are often used in the treatment of infections caused by CRE, although these isolates are in vitro resistant to carbapenems. A high-dose and continuous infusion of meropenem (2 g over 3 h, every 8 h) can maintain a serum concentration sufficient to achieve a bactericidal effect in strains with a MIC of 4-8 μg/ml for meropenem (55). Clinical studies prove that the inclusion of high-dose continuous infusion of meropenem to another active agent against KPC-producing bacteria improves the outcome of therapy, but only when the MIC for meropenem is < 8 μg/ml (45). However, a limitation of this combination is observed due to the often very high MICs of CRE isolates from blood cultures for meropenem (>16 μg/ml) (45, 56).

Ceftazidime-avibactam is the first combination agent to show activity against some CRE (57, 58). Despite its active potential against ESBLs and KPC-CRE (class A carbapenemase), the combination has no activity against MBL-producing bacteria (*K. pneumonia, P. aeruginosa and A. baumannii*)

(59). Ceftazidime-avibactam can be used in infections caused by MDR *P. aeruginosa* (60; 61). Conducted studies on mouse models show that the addition of avibactam to ceftazidime enhances the bactericidal effect on *P. aeruginosa* compared to ceftazidime alone (62). The recommended dose for MDR bacteria is 2000 mg/500 mg parenteral infusion for two hours every 8 hours.

A new opportunity for the therapy of infections, caused by MDR *P. aeruginosa* is the drug combination **ceftolozane-tazobactam**. According to literature data, approximately two-thirds of *P. aeruginosa* isolates resistant to broad-spectrum cephalosporins, piperacillin-tazobactam and meropenem are susceptible to this new antimicrobial agent (63). The standard dose for MDR-associated infections is up to 3 g every 8 hours.

The unique feature of **sulbactam**, a beta-lactamase inhibitor, which is commonly used in combination with other antimicrobials, is its activity against *Acinetobacter* spp. (53). The standard dosage is 4 g but in MDR *Acinetobacter* spp. infections, it is recommended to increase it to 9-12 g/day according to some authors (59).

The activity of **fosfomycin** against invasive CRE is well documented. In 80% of infections caused by CPR Gram-negative bacteria, eradication of the causative agent is observed. In addition, fosfomycin has a bactericidal effect on colistin-resistant microorganisms. A problem seen with the parenteral administration of fosfomycin is its difficult dosage. However, doses of 12 to 24 g per 24 hours in combination with another appropriate antibiotic are recommended (64). Oral administration in a dose of 3 g every 48-72 hours over a period of several weeks has demonstrated an impressive effect in lowering urogenital tract infections caused by resistant Gram-negative bacteria (65).

Aminoglycosides (gentamicin, amikacin, tobramycin) are broad-spectrum antibiotics that have a bactericidal effect on a large number of bacteria. Their broad-spectrum profile is enhanced when combined with other antimicrobials. The most successful and well-known combination is an aminoglycoside and an agent inhibiting the synthesis of peptidoglycan in the cell wall of bacteria (β-lactam antibiotics) (66). A disadvantage in the therapy of MDR infections is their nephrotoxicity and the low concentrations that are reached in the lung in sick patients, especially those with pneumonia (67).

Cefiderocol, eravacycline, plazomicin are new antimicrobial agents active in vitro against CPR bacteria but are still under investigation.

Cefiderocol is a siderophoric cephalosporin, which has the ability to bind iron ions. The resulting complex is actively transported into the bacterial cell through transport systems, which leads to the inhibition of cell wall synthesis (68). The activity of cefiderocol has been demonstrated in a large number of Gram-negative microorganisms, including CRE and MDR *P. aeruginosa* and *A. baumannii* (69). An additional factor improving the effectiveness of the drug against MDR bacteria is its high resistance to the hydrolyzing ability of carbapenemases. Cefiderocol has been tested on isolates producing KPC, NDM, IMP and VIM, with promising results. Its activity against OXA-beta-lactamases of *A. baumannii* and MBLs of *P. aeruginosa* has also been proven (70).

Eravacycline is a new synthetic fluorocycline belonging to the group of tetracyclines. The chemical structure, resembling that of tygecycline, successfully manages to bypass multiple resistance mechanisms that inactivate the older tetracyclines (efflux pumps, enzyme modification and protective proteins). In clinical studies, the agent demonstrated activity against representatives of the order *Enterobacterales* even those producing KPC, NDM and OXA beta-lactamases. The lack of activity against *P. aeruginosa* and *Burkholderia cepacia* complex should be taken into account (70).

Plazomicin is an aminoglycoside derivative designed to resist the aminoglycoside-modifying enzymes of Gram-negative bacteria (71). The spectrum of plazomicin is extended compared to amikacin, gentamicin and tobramycin. It is active against MDR enteric bacteria and those producing ESBLs and carbapenemases. In a study comparing the effect of plazomicin and meropenem in urinary tract infections caused by resistant bacteria, plazomicin has shown better results (67).

Imipenem-cilastatin-relebactam: relebactam is a piperidine beta-lactamase inhibitor designed to inhibit the activity of class A and class C beta-lactamases. Its addition to imipenem-cilastatin potentiates the bactericidal

effect of imipenem against carbapenemase-producing *E. coli*, *K. pneumoniae* and *Enterobacter* spp. A decrease in MIC has been reported for imipenem by up to 64-fold in KPC-producing *K. pneumoniae*. Unlike avibactam, the effect of relebactam on class D beta-lactamases is limited (72-74).

Meropenem-vaborbactam: vaborbactam is a cyclic derivative of boronic acid. Its advantages lie in its ability to inhibit class A, C and D beta-lactamases (75). The addition of vaborbactam to meropenem leads to a decrease in MIC of meropenem more than 16-fold in MDR enteric bacteria. A weak to no effect was reported against OXA-carbapenemases produced by *A. baumanni* and *P. aeruginosa* (70).

COLISTIN-RESISTANT BACTERIA

In recent years, worldwide, there has been an increase in the use of colistin not only in the treatment of infections caused by MDR Gram-negative bacteria but also in veterinary medicine and agriculture as a growth factor and protective agent. China is believed to be in the first place in the use of colistin (76). Overuse of this drug is accepted as an important factor in the emergence of resistance to it.

Due to the importance of the antibiotic as a strategic agent in CRE-induced infections, the lack of alternatives for therapy and probability for horizontal transmission of colistin resistance-associated genes, the emergence and spread of these strains are considered a threat to public health. Resistance to colistin is associated with the *mcr* genes (*mcr* 1-9), which are found in plasmids (76). For the first time, in China, in 2016, an *E. coli* isolate was identified, demonstrating resistance to colistin, which genetic determinant is located on a plasmid (77). The mechanism of resistance is associated with the modification of lipid A and a decrease in the negative charge of the outer membrane so the affinity of colistin decreases (76). Resistance to colistin/polymyxins varies across regions in Europe, with a gradual increase in bacteria, demonstrating a lack of susceptibility (78).

The growth of chromosomal and plasmid-mediated resistance to colistin in clinical CPR isolates from the *Enterobacteriaceae* family is a very worrying fact, as these isolates not infrequently demonstrate pan-drug resistance and practically have no alternatives for therapy (77, 79, 80).

A specific fact that should also be taken into account when using colistin is the phenomenon of heteroresistance. It is associated with the occurrence of reduced sensitivity or complete resistance to colistin in a subpopulation derived from colistin-sensitive microorganisms. Heteroresistance is believed to be due to *Pmr*AB mutation (81). Often this phenomenon is observed in *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* and is considered a potential problem (related to treatment failure) when using colistin for therapy of problematic infections (82). The impact of the phenomenon of heteroresistance to colistin in the treatment of complicated infections by MDR bacteria is still under investigation (81).
In addition to the phenomenon of heteroresistance, it should be mentioned that longer colistin therapy (more than 13 days), suboptimal dosing of the drug are also risk factors for the development of resistance.

VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE)

Resistance to vancomycin was first documented in the 1980s, with the first reports coming from England and France. A few years after its discovery, the incidence of VRE began to increase worldwide and became a life-threatening problem, especially in hospital settings. It is believed that patients with malignant diseases are most susceptible to VRE infection (83; 84). According to EARS Net data for 2019, the share of blood-derived VRE for Europe is 18.3%. For the same period, the rate of vancomycin non-susceptible invasive enterococci for Bulgaria is 21.1% (24).

The resistance of enterococci to glycopeptide antibiotics is due to the synthesis of modified peptidoglycan precursors that exhibit reduced affinity for vancomycin and teicoplanin. Six types of resistance are known, which are mediated by different genes (*vanA, vanB, vanC, vanD, vanE, vanG*) (85).

The expression of ***vanA*** is associated with a high degree of resistance to vancomycin (MIC 1024 μg/ml) and teicoplanin (MIC 512 μg/ml). It is usually seen in *Enterococcus faecium* and sometimes in *Enterococcus faecalis*. The lack of sensitivity is observed when enterococci acquire the ability to replace D-Ala-D-Ala with D-Ala-D-Lac. This structural change leads to the loss of hydrogen bonds between the substrate (amino acid sequence) and the antibiotic. This type of resistance in *E. faecium*

is linked to genes carried by a transposon Tn1546 (85).

VanB type resistance is characterized by a low degree of resistance to vancomycin (MIC 32 μg/ml) and preserved sensitivity to teicoplanin (MIC 0.5 μg/ml). It is observed in some strains of *E. faecium*. Resistance can be constitutive or inducible. Sometimes preserved sensitivity to teicoplanin can transform into resistance, the process includes two steps and requires prior loss of susceptibility to vancomycin with subsequent mutation in $vanS_B$ gene (85).

The species *E. gallinarum, E. casseliflavus* and *E. flavescens* demonstrate congenital resistance to vancomycin, but retain their sensitivity to teicoplanin. This susceptibility profile is typical of ***vanC*** carriers. Three varieties of *van* have been found for the *vanC* gene: *vanC*-1 (*E. gallinarum*), vanC-2 (*E. casseliflavus*) and *vanC*-3 (*E. flavescens*). The lack of effect when applying vancomycin in this type of resistance is due to the synthesis of peptidoglycan precursors ending in D-serine. *VanC* is chromosomally encoded, with constitutive expression but strains with inducible expression have also been found (85).

Type ***vanD*** is chromosomally encoded and constitutively expressed. It is characterized by resistance to vancomycin and variable for teicoplanin. No extraspecies or interspecies transmission of the genes responsible for this resistance profile have been documented (85).

VanG and ***vanE*** types are chromosomally encoded and inducible in nature. Associated with preserved sensitivity to teicoplanin, and a low rate of resistance to vancomycin. They are rare (85).

VRE, due to its high resistance to almost all standard antimicrobial drugs, represent a difficult pathogen to treat (86). Daptomycin and linezolid are the most commonly used agents for the therapy of invasive VRE infections (59). Due to the bactericidal effect and fewer side effects, daptomycin is often preferred over linezolid for VRE bacteremia in HSCT recipients. Linezolid is a bacteriostatic agent with a myelosuppressive effect and with the ability to slow down neutrophil engraftment in these patients (87). Despite these advantages of daptomycin, unfortunately, there are already reports of VRE resistant to the drug, especially in patients with hematological malignant diseases (88).

The increased susceptibility of individuals who have undergone HSCT to infectious agents, the high resistance of MDR bacteria, the expensive therapy of these infectious complications, and the high mortality require undertaking important measures. Efforts aimed at preventing complications should focus on reducing the risk of transmission of MDR microorganisms between patients in HSCT centers (59). Adherence to strict hand and environmental hygiene, strict adherence to recommendations for insertion and handling of intravascular catheters, prevention of contact between patients colonized with MDR bacteria and those without colonization are among the main measures (59, 89).

Another mechanism for reducing the proportion of MDR infections is the limited use of broad-spectrum antibiotics. Long-term use of broad-spectrum antimicrobials is a risk factor for the development of infections caused by MDR Gram-negative bacteria and VRE in cancer patients (41, 59, 90).

A de-escalation regimen of broad-spectrum antibiotics in stable patients without MDR isolates, daily assessment of the need for antibacterial therapy and optimization of the dose of the antimicrobials is an approach that ensures the reasonable use of antimicrobials in this high-risk group of patients (91).

Active screening for multidrug-resistant bacteria in patients undergoing HSCT may help identify high-risk individuals for developing MDR infections after transplantation, as well as speed up the therapeutic process when initiating empiric therapy when considering the microbiological results of this screening (59). For example, in a multicenter study in Italy involving HSCT patients, a high incidence of CPR *K. pneumoniae* infections was documented after colonization of the digestive system with such strains. These infections were observed in 26% of the colonized auto-HSCT and 39% of the allo-HSCT recipients (92).

CONCLUSION

The frequency of bacteria, demonstrating MDR is constantly increasing, and this phenomenon impairs the much-needed antimicrobial prophylaxis in patients with HSCT and hinders adequate and timely therapy. The lack of new antibacterial agents with activity against resistant bacteria predicts hard times for the clinicians responsible for treating these patients. Immediate actions are needed.

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