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Prophylaxis and treatment options for bacterial and fungal infections in recipients of hematopoietic stem cell transplantation: Brief review

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Abstract

Patients after hematopoietic stem cell transplantation are a risk group for developing various complications. Most of them are caused by infectious agents. Important in the post-transplant period is the prevention and therapy of these infectious complications, which often lead to high morbidity and mortality rates. The aim of this review is to present briefly the options for prevention and therapy of bacterial and mycotic infectious complications in these patients following hematopoietic stem cell transplantation.

Keywords: Hematopoietic stem cell transplantation; Bacteria; Fungi; Prophylaxis; Therapy

1. Introduction

The transplantation of hematopoietic stem cells is one of the revolutionary discoveries in the field of medicine, which led to the treatment of many diseases that were incurable until the middle of the last century [1, 2]. The medical conditions in which hematopoietic stem cell transplantation (HSCT) is used fall into two groups. The first group includes non-malignant conditions that lead to bone marrow failure, such as aplastic anemia, immunodeficiency syndromes, hemoglobinopathies and etc. The second group includes malignant, mainly hematological diseases such as acute and chronic leukemias, myelodysplastic syndrome, lymphomas, and multiple myeloma [1].

Due to a number of its specific features, HSCT is accompanied by the development of infectious and non-infectious complications. Infectious complications, which are among the leading causes of mortality in these patients, are associated with different types of bacteria, fungi, viruses and parasites [3], while non-infectious complications are due to the drugs used during the conditioning period and are most often presented as serositis, mucositis, veno-occlusive disease of the liver and lungs and hemorrhagic cystitis [4, 5]. *Styczynski* reported rates of bacterial, mycotic, and viral complications of 33.9%, 22.8%, and 38.3%, respectively [6]. The proportion of these complications is variable and depends on the type of transplantation, conditions at the transplantation center, geographic region, use of antimicrobials for prophylaxis, etc. [6]. The aim of this review is to present briefly the options for prevention and therapy of bacterial and mycotic infectious complications in these patients following hematopoietic stem cell transplantation.

2. Prophylaxis of bacterial infections

Prevention of infectious complications in the early periods of HSCT plays an important role. Oral quinolones are thought to reduce episodes of febrile neutropenia in allogeneic HSCT recipients. In the presence of mucositis in the oral cavity, the use of levofloxacin is preferred over ciprofloxacin, due to the wider spectrum of action and effectiveness against

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alpha-hemolytic streptococci, normal inhabitants of the oral cavity. Prophylactic use of quinolones has also been shown to reduce the incidence of infections caused by *Pseudomonas aeruginosa* [7].

Before and after stem cell infusion, antimicrobial prophylaxis plays an important role in the strategy to reduce the risk of infectious complications in the post-transplantation period. There are several types of prophylaxis.

In primary prophylaxis, antimicrobial agents are used to prevent infection in high-risk patients. Secondary prophylaxis uses prophylactic drug doses to protect against recurrent infections. The so-called preliminary therapy begins after screening with an appropriate method (most often Polymerase Chain Reaction, PCR) and aims to eliminate the infection before its progression to a clinically apparent disease [8]. Prophylaxis should begin as early as possible and along with the conditioning or stem cell infusion and continue throughout the period of neutropenia or until the risk of infection has passed.

During the early (neutropenic) period after HSCT, the main source of bacteria are the gastrointestinal tract and central venous catheter (CVC). The resident intestinal flora is responsible for infections caused by Gram-negative bacteria, while the catheter contributes to infections, associated with Gram-positive microorganisms [9].

A number of studies demonstrate that the administration of fluoroquinolones during this period leads to a decrease in mortality, febrile episodes and the risk of infections in neutropenic patients [8]. This type of prophylaxis is mainly used in allogeneic HSCT recipients. Antibacterial prophylaxis is also sometimes applied in autologous HSCT, when the conditioning regimen is myeloablative and there is a high degree of mucosal damage and immunosuppressive therapy is going to be initiated [8].

Before the 1980s, primary antimicrobial prophylaxis included the use of antimicrobial agents (gentamicin, vancomycin), which are usually not absorbed by the gastrointestinal tract and lead to the so-called "decontamination" of the digestive system, but due to the high cost and low compliance, the method was abandoned [9].

The European Conference on Infections in Leukemia recommends prophylaxis with fluoroquinolones throughout the period of neutropenia (10).

After engraftment (recovery of white blood cell count), late infections in the post-transplantation period are associated with immunosuppressive therapy and a chronic form of graft-versus-host-disease (GVHD) [11]. The presence of chronic GVHD, functional asplenia, immunosuppressive therapy and reduced synthesis of antibodies are prerequisites for the development of infections mainly due to encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis*) [12]. Therefore, antibiotics are used for primary prevention, which have a good effect against capsule-forming bacteria: penicillin, trimethoprim/sulfamethoxazole (TMP/SMX), levofloxacin [8]. Penicillin therapy is recommended for patients who are intolerant to TMP/SMX or amoxicillin 500 mg twice daily per os [11]. Prophylaxis should continue until immunosuppressive therapy is stopped [8].

2.1. Etiological therapy of bacterial infections

2.1.1. Genus Staphylococcus

Bacteria of the genus *Staphylococcus* are the most common Gram-positive microorganisms, associated with serious infections in patients after HSCT [13, 14].

S. aureus is a frequent commensal that is isolated in 10% - 40% of humans [15]. Colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) is considered an important risk factor among patients with HSCT and is a risk factor for the development of invasive staphylococcal infections [16]. For 2019 the proportion of MRSA isolates, associated with invasive infections (mainly bloodstream) in Europe is 15.5%, and in particular for Bulgaria - 14.4% [17]. Most of these infections in transplanted patients occur after disruption of the integrity of mechanical barriers, for example, during CVC insertion [18].

Currently, the treatment of infections caused by *S. aureus* is complicated by the emergence and spread of bacterial strains with multiple resistance. In cases where the causative agent has preserved sensitivity, antibiotics from the beta-lactam group are recommended as first-choice agents [19, 20]. Regarding the treatment of MRSA infection, vancomycin is considered the most optimal choice [21]. However, the use of vancomycin in MRSA-induced bacteremia as monotherapy is associated with a high risk of treatment failure, incomplete recovery and early relapse after discontinuation of therapy [22].

The duration of the therapy varies. After identifying the causative agent as Methicillin-resistant staphylococcus (MRS*),* parenteral therapy with vancomycin is recommended, and in case of preserved susceptibility of the isolate - the anti-staphylococcal drug from the group of penicillins or cefazoline is used [23]. In patients with uncomplicated catheter-associated bloodstream infections (CABSI), a minimum of 14 days long therapy is recommended when *S. aureus* is isolated and 7 day for coagulase-negative staphylococci (CoNS) [24]. All catheters, associated with bloodstream infection should be removed due to the fact that they are colonized. An exception is uncomplicated CABSI caused by *S. aureus*, when the catheter is permanent or reinsertion of a new one is not possible. In these cases, lock therapy is recommended [23].

If *S. aureus* is suspected as the cause of the infection and until the microbiological result is obtained, it is recommended to lower the level of immunosuppression, find the source or the primary focus of the infection and, if possible, remove it (foreign bodies, abscesses, necrotic matter), as well as start empiric therapy. After receiving a final microbiological result, treatment should be tailored to the result of the antibiogram [25].

Representatives of the CoNS group are part of the resident human flora. Approximately 90% of individuals are colonized by various CoNS species [22]. Unlike the general population, HSCT recipients are at risk of developing invasive infections caused by CoNS. This is due to disruption of the protective barriers after CVC insertion, operative wounds, presence of severe mucositis of the oro-intestinal area after the conditioning regimen in allogeneic HSCT or periodontal disease during neutropenia in the pre-engraftment period [26 – 28]. The most frequently isolated staphylococcus from the CoNS group that leads to invasive infections in immunocompromised individuals is *S. epidermidis* [29].

A large number of studies have reported the dominance of CoNS as causative agents of bloodstream infections over those caused by *S. aureus*. A particularly major difference was observed in neutropenic patients with an inserted CVC. Moreover, MRS from the skin flora are more prone to cause bloodstream infections than those demonstrating susceptibility. The proportion of CABSI caused by MRS from the CoNS group is higher than the ones caused by MRSA – 93% vs. 23% respectively [30]. For this reason, the initiation of empiric therapy with vancomycin in neutropenic patients with CVC is recommended (2g/24 hours) [23].

2.1.2. Genus Streptococcus

Streptococci are a large heterogeneous group, which nomenclature is constantly undergoing changes [31]. Group alpha-hemolytic streptococci (VGS) includes a large number of different species of streptococci, which are often isolated from the oro-intestinal tract, upper respiratory tract and female urogenital system [32]. The most frequently isolated bacteria from the group, responsible for the development of invasive infections in transplanted patients and individuals with severe neutropenia belong to the *mitis* group and include *S. mitis, S. gordonii, S. oralis, S. sanguis* and *S. parasanguis* [33 – 35].

VGS bloodstream infections are seen almost exclusively in patients receiving aggressive chemotherapy for the treatment of acute leukemias and individuals being conditioned for allo-HSCT [36]. It is believed that the disruption of the mucosal barrier of the gastrointestinal tract is the greatest risk factor for the development of invasive infection, allowing these bacteria with low virulence to enter the blood circulation [37].

In addition, the widespread use of prophylactic antibiotics that have limited effect on VGS (fluoroquinolones and TMP/SXT) also play an important role in the emergence of invasive infections [38].

The high resistance of VGS to beta-lactam antibiotics is an obstacle and limits the choice of an appropriate antimicrobial agent for treatment [39, 40]. Only a small proportion of VGS, isolated from neutropenic patients, are in vitro susceptible to penicillins [41]. In the presence of susceptibility to penicillins, these antibiotics appear as the first choice for therapy. The susceptibility of clinical VGS isolates to vancomycin is preserved in almost 100% [42].

2.1.3. Genus Enterococcus

Enterococci are other representatives of Gram-positive bacteria and cause much more frequent infections in immunosuppressed cancer patients and individuals with HSCT compared to the general population [43]. They occur as part of the normal bacterial flora of the gastrointestinal tract. Of these, *E. faecalis* and *E. faecium* are the most frequently isolated species [44]. Patients with hematological malignancies and undergoing HSCT have a high incidence of intestinal colonization and subsequent risk of developing invasive diseases due to vancomycin-resistant enterococci (VRE) [45].

The therapy of infections caused by enterococci is difficult due to the demonstrated antimicrobial resistance. Most of the clinically relevant *E. faecalis* isolates demonstrate in vitro sensitivity to widely used beta-lactam antibiotics such as

penicillin, ampicillin, amoxicillin, piperacillin and imipenem. It is important to note that enterococci have innate resistance to antibiotics from the group of cephalosporins and clindamycin. Unlike *E. faecalis, E. faecium* in more than 50% of cases demonstrates resistance to penicillins [46]. Macrolides and TMP/SXT are also not effective in the therapy of enterococcal infections [47]. In the presence of patient hypersensitivity to beta-lactam antibiotics or resistance to them, vancomycin is the first-line antibiotic [48]. In the presence of sensitivity to beta-lactam antibiotics and aminoglycosides, combined therapy (beta-lactam + aminoglycoside) is recommended in order to achieve synergism [49].

In cases of VRE-associated infection, the antimicrobial agent of choice is linezolid. The recommended dose is 600 mg IV every 12 hours. In invasive infections that occur in severely immunosuppressed individuals and those with HSCT, monotherapy with linezolid has been reported to be effective [50]. However, strains of VRE that are also resistant to linezolid are now being reported. In a study conducted in 2014 – 2015 in Germany, VRE-non-susceptible to linezolid were isolated from 20 patients, 18 of them after HSCT [51].

2.2. Order *Enterobacterales* and Gram-negative non-fermenters (GNNF)

Aerobic Gram-negative bacteria are responsible for 15-20% of monobacterial infections in neutropenic patients, including patients with hematological malignancies and those with HSCT [13, 52], and in the latter group of patients they are associated with significant mortality [53, 54]. Infections due to these bacteria can affect any anatomical area: urinary tract, blood, respiratory tract, digestive system, skin, etc. Risk factors leading to the development of invasive Gram-negative infections in neutropenic individuals are age over 45 years, recent therapy with beta-lactam antibiotics, symptoms from the urinary tract, failure to decontaminate the digestive system with aminoglycosides [55] and intestinal colonization before the transplantation [56].

This group of bacteria includes representatives of the order *Enterobacterales* and aerobic GNNF (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Bulkholderia* spp. and others). In the last two decades, bacteria belonging to the family *Enterobacteriaceae* are among the most important opportunistic pathogens causing infections in patients with HSCT. The family includes a wide variety of bacterial species: *Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Salmonella* spp., *Shigella* spp. and others [57].

Rapid recognition of infections caused by Gram-negative enteric bacteria and prompt initiation of antimicrobial therapy is critical. Removal of the focus of infection (if known) is strongly recommended: catheter removal, drainage of abscess when possible. It is recommended that when choosing an antimicrobial agent to start empiric therapy, the epidemiological profile of resistance of enteric bacteria in the relevant medical institution or region should be taken into account, and that definitive therapy should be undertaken after antimicrobial susceptibility testing [57]. Drugs that are active against this group of bacteria are beta-lactam/beta-lactamase inhibitor (amoxicillin/clavulanate, piperacillin/tazobactam), other beta-lactams (cephalosporins and carbapenems), fluoroquinolones, aminoglycosides and TMP/SXT.

2.2.1. Pseudomonas aeruginosa

Since the 1990s , *Pseudomonas aeruginosa* has established itself as one of the frequent causes of bacterial infections in neutropenic patients. Before the advent of antimicrobial drugs with an anti-pseudomonal effect (carbenicillin), infections due to *P. aeruginosa* were associated with a mortality rate exceeding 90%. After the introduction of aminoglycosides, anti-pseudomonal penicillins, cephalosporins and carbapenems, a drastic drop in mortality to less than 20% was observed [58]. The gold standard for therapy of infections caused by *P. aeruginosa* is the combination of anti-pseudomonal beta-lactam (piperacillin, piperacillin/tazobactam, ceftazidime) and aminoglycoside. Concomitant administration of quinolones and beta-lactams is sometimes used, but clinical data supporting this combination are scarce [59]. In severe pseudomonal infections, a higher than the standard dose of the quinolone is recommended: ciprofloxacin 3 x 400 mg instead of 2 x 400 mg or levofloxacin - 750 mg instead of 500 mg [59].

2.2.2. Stenotrophomas maltophilia

Over the last two decades, there has been an increase in the incidence of colonization and infections caused by *S. maltophilia* in cancer patients and those after HSCT [60]. Patients with prolonged neutropenia treated with broad-spectrum antibiotics, especially carbapenems, and those requiring mechanical ventilation are at the highest risk of *S. maltophilia* infection [61 - 63]. In Bulgaria, studies on the antibacterial susceptibility of *S. maltophilia* isolates, obtained from patients with oncological diseases, have been conducted since the 1990s [64]. The most common manifestations of *S. maltophilia* infection in HSCT are bacteremia, which is often due to an indwelling catheter, tracheitis and pneumonia [63]. Colonization of the skin and digestive tract is a common condition, especially in patients with prolonged

hospitalization. Intestinal colonization with *S. maltophilia* can also be observed after prophylaxis with fluoroquinolones [60]. In a conducted study, the intestinal colonization was detected in 10% of hospitalized patients with neutropenia [65]. The sulfonamide TMP/SMX, at maximum dose, is the antimicrobial agent that is available as agent of first choice for *S. maltophilia* infections, but isolates resistant to this agent have been reported in the literature [63, 66 - 68]. In our country, resistant to TMP/SMX strains have also been reported [69, 70].

Alternatively, in cases of TMP/SXT–resistant infections, ticarcillin/clavulanate, ceftazidime, ciprofloxacin and levofloxacin can be used [71].

2.2.3. Acinetobacter spp.

Genus *Acinetobacter* is a heterogeneous group consisting of over 50 bacterial species widely distributed in nature. Human infections are mainly caused by the species *A. baumannii* and less common by *A. colcoaceticus* and *A. lwofii* [72]. *Acinetobacter baumannii* is a typical nosocomial pathogen, isolated mainly in intensive care units from severely ill patients with impaired integrity of protective barriers. Infection with this coccobacillus is manifested in a large percentage of the cases as pneumonia and bacteremia. Less common are urinary tract infections (mainly when a catheter or percutaneous nephrostomy are used), postoperative meningitis and wound infections [73]. This microorganism is associated with high morbidity and mortality (41.9%) in patients with hematological malignancies and neutropenia [74 -77]. Average frequency of infections associated with *A. baumannii* worldwide is approximately 1,000,000 cases per year [78]. Risk factors for *A. baumannii* infection, bacteremia, and colonization include burn, surgical wounds, CVC, severe underlying disease, especially oncohematological, long-term broad-spectrum antimicrobial therapy and endotracheal intubation [79].

Traditionally imipenem and sulbactam are the antibiotics with the best activity against *A. baumannii* [80]. Other therapeutic options are the use of aminoglycosides, quinolones and TMP/SMX. A serious problem in infections associated with *A. baumannii* is the increasing proportion of strains acquiring resistance to different groups of antimicrobial agents, including those with multiple and pandrug-resistance. Currently, the largest share is *A. baumannii,* demonstrating resistance to beta-lactam antibiotics, a phenomenon due to the production of a wide range of beta-lactamases that hydrolyze penicillins, cephalosporins and carbapenems [81, 82]. Among the few treatment options for carbapenem-resistant *A. baumannii* infections are polymyxins (colistin) and tigecycline. Unfortunately, colistin-resistant strains have also been reported [83]. Other antibiotics, such as minocycline, TMP/SMX, rifampin, fosfomycin are also used, but usually as part of combination therapy [83].

Similar to bacterial infections, mycotic complications after HSCT are also the cause of high mortality (40% - 90%) [84]. The frequency of mycotic infections after transplantation depends on the duration of the neutropenic period, the type of transplantation, applied prophylaxis, the geographical region and ranges from 10% to 20%. The likelihood of developing mycotic infection is higher in allogeneic HSCT recipients, especially those receiving immunosuppressants [84].

2.3. Prophylaxis of fungal infections

Primary prophylaxis of fungal infections involves administration of an antifungal agent to prevent the development of infection in high-risk recipients [8]. The gold standard for the prevention of such infections is fluconazole, which reduces mortality in allo- and auto-HSCT. Fluconazole has an effect on *Cryptococcus* spp. and most *Candida* spp., except *C. krusei* and some strains of *C. glabrata* [9]. Agents with activity against filamentous fungi are voriconazole, posaconazole and amphotericin B [8].

There are various schemes for the prevention of mycotic infections:

- Fluconazole 200 to 400 mg daily
- Voriconazole 6 mg/kg IV every 12 hours as initial dose and then 4 mg/kg IV every 12 hours followed by 200 mg orally every 12 hours
- Posaconazole 200 mg orally three times a day [11].

Patients with hematological malignancies have a higher risk of developing pneumonia caused by *Pneumocystis jirovecii* than those with solid tumors. Therefore, it is recommended to prescribe prophylaxis no later than 30 days after transplantation, which should last at least one year [11]. The most effective combination for prophylaxis against *Pneumocystis* pneumonia is TMP/SMX (80/400 mg daily) [11]. Prophylaxis should continue until the CD4+ count reaches 200 - 400x10^6 /L [9]. Prophylaxis with TMP/SMX also prevents the development of infection with *Toxoplasma gondii, Nocardia* spp., as well complications caused by susceptible strains of *S. pneumoniae* and *H. influenzae* [11].

The introduction of antifungal prophylaxis with fluconazole has been shown to be effective approach and reduces the incidence of *C. albicans* among this group of patients, but leads to the selection of fluconazole-resistant fungi such as *C. kruzei* and *C. glabrata* [84]. Risk factors for developing invasive fungal infection are associated with donor type, GVHD, high-dose corticosteroid therapy, high ferritin levels, etc. [85, 86 – 88].

2.4. Therapy of fungal infections

The most commonly used antimycotic agents for the therapy of invasive mycotic infections belong to the group of echinocandins and azoles. Amphotericin B gives way to caspofungin, anidulafungin and fluconazole, because of its increased toxicity and remains the agent of second choice [89].

In patients with candidemia, initial therapy with echinocandins in the following dosage is recommended:

- 200 mg loading dose, then 100 mg IV daily for anidulafungin
- 70 mg loading dose, then 50 mg IV daily for caspofungin [8]

Fluconazole is an alternative to the echinocandins and can be used in patients who are not critically ill and in whom fluconazole-resistant fungi are not expected to be isolated. The standard dosage is 800 mg (12 mg/kg) as a loading dose, followed by 400 mg (6 mg/kg) orally or parenterally daily. Due to the good bioavailability of fluconazole, oral administration is recommended. In case adequate intestinal absorption is not expected or the patient is in a severe condition, it can also be administered parenterally. In the event of resistant mycotic isolates and allergic reactions to these agents, liposomal forms of amphotericin B can be included in the therapeutic regimen, despite the possibility of toxic manifestations (3 – 5 mg/kg daily) [90, 91] Recommendations of Infectious Diseases Society of America from 2016 advise continuing the therapy for at least two weeks after negative blood cultures. Daily or every other day monitoring of blood cultures is also recommended. The presence of a metastatic focus (abscess or endocarditis) should be considered in cases of long-lasting positive blood cultures on the background of therapy [90]. As an initial therapy for invasive pulmonary aspergillosis (IPA) voriconazole or isavuconazole monotherapy is recommended in most patients, but in particularly severe cases, the addition of an echinocandin to voriconazole is recommended [92]. For patients showing intolerance to voriconazole, monotherapy with isavuconazole is accepted as an alternative.

The recommended dose of voriconazole for the treatment of IPA is 6 mg/kg IV on day 1 and 4 mg/kg IV every 12 hours for the remaining days [93]. The isavuconazole regimen involves administration of 372 mg isavuconazole sulfate (equivalent to 200 mg isavuconazole base) as a loading dose every 8 hours for 6 doses (48 hours total) orally or parenterally, followed by 372 mg once daily starting 12 to 24 hours after the last loading dose [93].

Other antimycotic agents that are effective against molds and may be included as alternative therapy for IPA are echinocandins and amphotericin B in the following dosages: caspofungin 70 mg IV on the first day and 50 mg IV thereafter; anidulafungin 200 mg IV on the first day and 100 mg IV thereafter; liposomal amphotericin B – 3-5 mg/kg per day [93]. The minimum duration of the therapeutic regimen in cases of IPA is between 6 and 12 weeks [94].

3. Conclusion

Patients after HSCT are prone to severe and life-threatening infections. Knowing how to prevent and treat these complications is of crucial importance.

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