Artigo Especial / Special Article

Resistant bacteria in stem cell transplant recipients

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Bacterial infections account for most infections in hematopoietic stem cell transplant recipients. While early mortality reduced dramatically with the introduction of the concept of empirical antibiotic therapy in neutropenic patients, no effect of prophylaxis on the mortality was observed in many studies. On the other hand, antibiotic prophylaxis has resulted in the emergence of resistance among bacteria. In addition, the choice of the antibiotic regimen for empirical therapy and the practices of antibiotic therapy during neutropenia may result in a significant shift in the pattern of bacterial infections. The use of quinolones and vancomycin as prophylaxis, and of carbapenems and vancomycin in the empirical antibiotic therapy, are associated with the appearance of resistant Gram-positive and Gram-negative bacteria. Therefore, hematologists must be aware of the impact of these practices on the emergence of infections due to multi-resistant pathogens, since these infections may be associated with increased mortality.

Rev.bras.hematol.hemoter., 2002, 24(3):220-227

Key-words: Bacterial infection, antibiotic, resistance, bone marrow transplant

Introduction

Hematopoietic stem cell transplantation (HSCT) has become standard treatment for many malignant and non-malignant diseases. A major drawback for the success of HSCT is the development of infectious complications, which are associated with significant morbidity and mortality (1, 2). Bacterial infections account for most infections in HSCT recipients; between 10 and 59% of these patients have at least one episode of bacteremia (3). Antibacterial prophylaxis and empirical therapy have helped to reduce the incidence (prophylaxis) and mortality (empirical therapy) associated with such infections. However, bacterial resistance has become a major problem. In this article we will discuss the impact of prophylactic and therapeutic measures on the development of resistance, and the consequences of this problem to HSCT recipients.

Risk factors and pathogens causing bacterial infections in HSCT recipients

Bacterial infections occur both in the pre-engraftment and in the post-engraftment period. The risk factors and etiologic agents differ in these periods. In the pre-engraftment period, the major risk factors for bacterial infections are neutropenia, mucositis and the presence of a central venous catheter. Since all these factors are present in both allogeneic and autologous stem cell transplant, the incidence and
species distribution do not differ significantly between these two modalities of transplant (4). Although in most centers Gram-positive organisms (especially coagulase-negative staphylococci and streptococci) account for the majority of bacteria causing bloodstream infections in HSCT recipients (5), the distribution of bacteria causing infection during the early post-transplant period may vary substantially among different centers, and over time. In a study of bacteremias in 519 HSCT recipients from a single institution, Gram-positive and Gram-negative bacteria accounted for 62% and 38% of bacteremias (6). The rates of bloodstream isolates reduced over a 7-year period, but since the reduction was more pronounced among Gram-positive organisms, the ratio of Gram-positive to Gram-negative organisms dropped from 2.7 to 1.3. However, other centers have witnessed a real increase in Gram-negative bacteremia, including infection due to *Pseudomonas aeruginosa* (7).

In the post-engraftment period, most bacterial infections occur in allogeneic HSCT. This period may be divided in early and late post-engraftment phases. In the early post-engraftment phase, the major risk factors for bacterial infection are the presence of a vascular catheter, and mucosal breakdown caused by acute graft-versus-host-disease (GVHD) (8). Bacteria responsible for infection in this period include both Gram-positive and Gram-negative organisms, and the severity of such infections is much lower than in the pre-engraftment period, because neutropenia is no longer present. In the late post-engraftment phase, defects in the humoral immunity predominate, and their severity is proportional to the severity of chronic GVHD (8). The major pathogens in this period are encapsulated bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides* (4).

### Use of antibiotics in HSCT recipients

Considering the risks and epidemiology of bacterial infections in HSCT, different strategies of antibiotic use have been employed. These include the use of antibiotics as prophylaxis, empirical therapy, and treatment of documented infections.

#### Antibiotic prophylaxis

**Pre-engraftment period**

The prophylactic use of antibacterial agents has been extensively studied in neutropenic patients. Since Gram-negative bacteremia may cause life-threatening infection in HSCT recipients during this period, the quinolones have been considered the agents of choice. Indeed, over the past 15 years, several studies have evaluated the efficacy of these agents, and documented a significant reduction in the incidence of Gram-negative bacterial infections (9). However, quinolone prophylaxis did not result in a reduction in the duration of fever and, more importantly, in infection-related mortality. However, an even greater limitation for the use of quinolones in the prophylaxis of bacterial infections during the pre-engraftment period of HSCT is the emergence of resistance (10,11,12). In a study of the patterns of bacterial susceptibility to antibiotics in HSCT recipients, the frequency of resistance to quinolones among Gram-positive and Gram-negative bacteria (especially *Enterobacteriaceae* and *P. aeruginosa*) increased significantly after the introduction of these agents in the prophylactic regimen (13). In another study that evaluated the incidence and susceptibility of blood isolates during 7 years in a HSCT unit, streptococci were the most frequent bacteria causing infection, and increasing resistance to penicillin, ciprofloxacin and imipenem was observed among these organisms (6). Although antibacterial prophylaxis (mostly ciprofloxacin) was associated with a reduction in the incidence of infection, it resulted in an increase in resistance to beta-lactam antibiotics. The widespread use of quinolones has also been associated with a significant increase in resistance to quinolones of coagulase-negative *Staphylococcus* (14).

Interestingly, we have observed a reversion of susceptibility of *Escherichia coli* to quinolones after having discontinued its use in the prophylaxis of neutropenic patients. Between 1992 and 1997, quinolones were used in 43% of 420 episodes of fever and neutropenia, but in only one of 433 episodes between 1998 and 2001. The frequency of Gram-negative and Gram-positive bacteremia were
similar in the two periods, but the frequency of bacteremia due to quinolone-resistant E. coli was 60% in period 1 and 6% in period 2 (p=0.02) (data not published). Therefore, although the use of quinolones in the prophylaxis of bacterial infections is routine in many HSCT centers, its use should be re-evaluated, considering the risks of induction of resistance. Furthermore, as many HSCTs are performed on an outpatient basis or with early discharge, quinolones are suitable drugs for oral empirical antibiotic therapy. A recently published guideline for prevention of infection in HSCT recipients does not recommend the routine use of antibacterial prophylaxis, with a “DIII” level of evidence (moderate evidence against efficacy, with evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees). It is also recommended that if physicians choose to use prophylactic antibiotics, they should routinely review hospital and HSCT center antibiotic susceptibility profiles (15).

Another strategy that has been widely used in many HSCT centers is to give betalactam antibiotics intravenously to afebrile neutropenic patients. Although this strategy may be associated with a slight reduction in the incidence of infection (16), it has a tremendous negative impact on the emergence of resistance. In a study that evaluated bacterial susceptibility in a 7-year period in a HSCT unit (6), the frequency of use of betalactam antibiotic in afebrile patients increased from less than 10% in 1991 to 57% in 1997. Although imipenem had never been used for this purpose and its use remained constantly low (only 14% of patients) during the study period, the frequency of streptococcal resistance to this agent increased from zero prior to 1996 to 25% in 1996 and 1997. Considering that betalactams are the main antibiotic class used in the empirical antibiotic therapy (a strategy that results in a significant reduction in mortality), the emergence of resistance to betalactam antibiotics is clearly a major concern. The use of third-generation cephalosporins has also been associated with an increase in the frequency of extended-spectrum betalactamase (ESBL)-producing Gram-negative organisms (17). Therefore, the use of betalactam antibiotics to afebrile neutropenic patients has no scientific basis and must be strongly discouraged.

Prophylaxis of infection against Gram-positive organisms has also been studied both with oral and intravenous agents. In a study in HSCT recipients, patients were randomized to receive ciprofloxacin with or without intravenous vancomycin. No significant differences in the frequency of bacteremias were observed (18). In another randomized study, the use of vancomycin resulted in a significant reduction in the frequency of Gram-positive infections and duration of fever and antibiotic use (19). Considering the controversial results of these studies and, more importantly, the impact of vancomycin use on the development of resistant of Gram-positive bacteria, particularly vancomycin-resistant Enterococcus (VRE - see below), its use is not justifiable.

Oral agents, such as penicillin, macrolides or vancomycin, have also been used as prophylaxis in neutropenic patients. In a randomized study, patients received pefloxacin plus penicillin (268 patients) or placebo (268 patients) (20). The frequency of fever and Gram-positive bacteremia was significantly higher in the placebo group. However, 14 patients in the penicillin arm developed streptococcal bacteremia, and 46% of isolates were resistant to penicillin. Resistance to penicillin has been increasingly reported among streptococcal isolates from HSCT recipients (6), and is associated with the use of penicillin. This is particularly important because a) the frequency of viridans streptococcal bacteremia has increased in the last decade; b) viridans streptococcal bacteremia occurs in patients with severe mucositis, and may be associated with a rapidly fatal clinical picture of respiratory failure and shock; and c) the higher the rate of resistant to penicillin, the more frequent is the use of empirical vancomycin in patients with severe mucositis.

Considering the marginal benefit and these concerns, the role of anti-Gram-positive prophylaxis must be questioned. Indeed, a meta-analysis that evaluated the usefulness of anti-Gram-positive prophylaxis in neutropenia patients showed that although there was a significant reduction in the frequency of infection by Gram-positive bacteria, there was no benefit in terms of fever-related morbidity or infection-related mortality (21).
**Post-engraftment period**

Antibacterial prophylaxis is not usually given in the early post-engraftment phase, because the risk of infection is low. In the late post-engraftment phase there is an increased risk of infection due to encapsulated bacteria, the risk being proportional to the severity and duration of chronic GVHD. Oral penicillin or sulphamethoxazole-trimethoprim has been given to these patients and their use is generally accepted, even though there are no controlled clinical trials supporting this recommendation. In the guidelines for prevention of infection in HSCT recipients (15), it is recommended that these antibiotics be used in patients with chronic GVHD for as long as treatment for GVHD is administered, with a "BIII" level of evidence (strong or moderate evidence for efficacy, with evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees). This situation is far different from antibiotic prophylaxis during neutropenia. While during neutropenia prophylaxis do not impact on survival provided prompt empirical antibiotic therapy is started once the patient becomes febrile, pneumococcal bacteraemia may be rapidly fatal. Therefore, the consequences of no intervention overweight those related to the chronic use of penicillin, i.e., the development of penicillin-resistance. Yet, physicians must be aware that resistance correlates with the duration of prophylaxis.

**Empirical antibiotic therapy**

Empirical antibiotic therapy is standard in the treatment of febrile neutropenic patients since the early 80s. This strategy resulted in a dramatic reduction in early death rate, something from 80 to less than 20%. Over the past 20 years a large number of randomized clinical trials have compared different antibiotic regimens and strategies of empirical therapy. Overall no regimen proved unequivocally superior in terms of success with or without modifications of the empirical regimen or death. With the introduction of antibiotics with good anti-pseudomonal activity, the practice of monotherapy has increased in the last decade. According to recently published guidelines for the use of antibiotics in neutropenic patients, accepted antibiotics to be used in monotherapy are ceftazidime (third generation cephalosporin), cefepime (fourth generation cephalosporin), and the carbapenems (meropenem or imipenem) (7).

In addition, piperacillin-tazobactam, an anti-Pseudomonas penicillin, is equally effective (22). If no regimen or agent is clearly superior, what are the parameters to guide the choice of a particular regimen? Are there considerations regarding resistance that may be taken into consideration? The first consideration in choosing the antibiotic regimen to be given empirically to neutropenic HSCT recipients is the knowledge of the type, frequency, and antibiotic susceptibility of bacterial isolates that predominate in a particular hospital. In other words, the frequency, distribution and susceptibility patterns of an HSCT unit are a reflection of what happens in the hospital as a whole. Institutions with high frequency of ESBL-producing enterobacteria should probably remove third generation cephalosporins from the empirical regimen, even if it works (and it usually works!) for most patients at that unit, since the emergence of ESBLs may be related to the use of these agents (17).

On the other hand, the emergence of bacteria with lower pathogenicity, such as Acinetobacter spp. and Stenotrophomonas maltophilia is a concern (6, 23), and may be associated with the widespread use of antibiotics with very broad spectrum activity, such as carbapenems (24). However, because P. aeruginosa is still the bacteria associated with the highest mortality among neutropenic HSCT recipients (6), the choice of the empirical regimen must predominantly take into account the susceptibility profiles of this bacteria at a particular institution. Therefore, the regimen must be one that is very active against P. aeruginosa, but also strategically omits a particular antibiotic that may be associated with the development of resistance. This is particularly true for the carbapenems, since their use is associated with the appearance of multi-resistant strains of P. aeruginosa (25), particularly in immunosuppressed individuals (26). The use of carbapenems is also a risk factor for candidemia in neutropenic patients (27). In addition to the judicious use of antibiotics during neutropenia, every effort to control the horizontal transmission...
Table 1: Antibacterial practices in hematopoietic stem cell recipients associated with the appearance of resistance

<table>
<thead>
<tr>
<th>Practice</th>
<th>Resistance problem</th>
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<tr>
<td>Use of quinolones in afebrile neutropenic patients</td>
<td>Quinolone-resistant <em>P. aeruginosa</em></td>
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<tr>
<td></td>
<td>Quinolone-resistant <em>E. coli</em></td>
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<td></td>
<td>Quinolone-resistant <em>Enterobacter</em> sp.</td>
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<td></td>
<td>Quinolone-resistant <em>Streptococcus</em> sp.</td>
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<td></td>
<td>Quinolone-resistant coagulase-negative <em>Staphylococcus</em></td>
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<tr>
<td>Use of betalactam antibiotics in afebrile neutropenic patients</td>
<td>Carbapenem-resistant <em>streptococci</em></td>
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<td></td>
<td>ESBL-producing <em>enterobacteria</em></td>
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<tr>
<td>Use of intravenous vancomycin in afebrile neutropenic patients</td>
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<tr>
<td>Use of penicillin in afebrile neutropenic patients</td>
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<td>Use of penicillin in afebrile HSCT recipients with chronic GVHD</td>
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<tr>
<td>Use of third-generation cephalosporins in the empirical treatment of neutropenic patients</td>
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<td>Use of carbapenems in the empirical treatment of neutropenic patients</td>
<td>Multi-resistant <em>P. aeruginosa</em></td>
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<td></td>
<td>Multi-resistant <em>Acinetobacter</em> sp.</td>
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<td>Multi-resistant <em>Stenotrophomonas maltophilia</em></td>
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<td>Use of vancomycin in the empirical treatment of neutropenic patients</td>
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<td></td>
<td><em>Staphylococcus aureus</em> with intermediate sensitivity to vancomycin</td>
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<td><em>Candidemia</em></td>
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<td></td>
<td>Vancomycin-resistant <em>Enterococcus</em></td>
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</table>

ESBL - extended-spectrum betalactamase; HSCT - hematopoietic stem cell transplant; GVHD - graft-versus-host-disease

and spread of resistant organisms in the HSCT unit is crucial, since persistent carriage of resistant bacteria has been reported in HSCT units (28).

Glycopeptides (vancomycin and teicoplanin) have been used in febrile neutropenic patients either upfront or in persistently febrile patients. The strongest argument favoring the use of these agents in the initial antibiotic regimen is the possibility that the patient develops a bacteremia due to a penicillin-resistant isolate of viridans *Streptococcus*, since bacteremia due to these agents may be fatal. On the other hand, there are many arguments against their use, including toxicity and the emergence of resistance. The use of vancomycin has been associated with the development of infections due to glycopeptide-resistant coagulase-negative *staphylococci* (29), coagulase-positive *staphylococci* with intermediate sensitivity to glycopeptides (GISA – “glycopeptide-intermediate *Staphylococcus aureus*”) (30) and *Candida* (27).

However, the most dramatic problem related to the overuse and misuse of vancomycin was the world wide appearance of VRE (31). Because of the close association between vancomycin use and VRE, the Infectious Diseases Society of America’ guidelines for the
use of antimicrobial agents in neutropenic patients recommend that vancomycin be used in the initial empirical antibiotic regimen only in the following situations: clinically suspected serious catheter-related infections, known colonization with resistant isolates (penicillin- and cephalosporin-resistant pneumococci or methicillin-resistant S. aureus), positive results of blood culture for Gram-positive bacteria before final identification and testing, or hypotension (7). Regarding viridans Streptococcus, although penicillin resistance has increased, antibiotics such as cefepime, piperacillin-tazobactam and carbapenems have good activity against the majority of strains. In addition to the exclusion of vancomycin from the initial empirical antibiotic therapy in most instances, the empirical addition of vancomycin after 2 or 3 days of persistent fever is not recommended, unless any of the criteria mentioned above is present (7). VRE has been described in HSCT recipients (32), and the appearance of VRE in a HSCT unit must be avoided. Therefore, empirical use of vancomycin should be restricted. We have had a good experience in reducing the use of vancomycin in our neutropenic patients by following the guidelines and introducing fourth generation cephalosporins in the empirical antibiotic regimen (33). With this strategy, the use of vancomycin reduced from 73 to 43% of febrile episodes.

Conclusion

Bacterial infections are frequent in HSCT recipients, and are associated with significant morbidity. While early mortality reduced dramatically with the introduction of the concept of empirical antibiotic therapy in neutropenic patients, no effect of prophylaxis on the mortality was observed in these studies. On the other hand, these practices have resulted in the emergence of resistance among Gram-positive and Gram-negative organisms. In addition, the choice of the antibiotic regimen for empirical therapy and the practices of antibiotic therapy during neutropenia may result in a significant shift in the pattern of bacterial infections. Table 1 lists the main problems of resistance in HSCT recipients and the practices that are considered to have contributed to resistance.

The emergence of resistance may increase mortality, as evidenced by studies that showed that infections caused by resistant organisms are associated with higher death rates (17, 34, 35, 36). Therefore, hematologists must be aware of these problems, and the negative impact of practices that may work in a single patient, but may shift the microbial patterns of infection overall, compromising the outcome of other patients.

Bacteria resistentes nos receptores do transplante de células precursoras hematopoéticas
Marcio Nucci

Resumo

As infecções bacterianas são muito frequentes em receptores de transplante de células tronco hematopoéticas. Enquanto que a mortalidade precoce associada a estas infecções reduziu dramaticamente com a introdução do conceito da terapia antibiótica empírica no paciente neuropênico febril, nenhum impacto na mortalidade foi observado nos estudos de profilaxia antibacteriana. Por outro lado, o uso de antibacterianos na profilaxia tem resultado na emergência de infecções por bactérias resistentes, razão pela qual a profilaxia tem sido abandonada. Além disso, a escolha do esquema antibiótico empírico e as práticas de terapia antibiótica durante a neutropenia podem resultar em mudanças nos padrões de infecções bacterianas. O uso de quinolonas e vancomicina na profilaxia, e de carbapenems e vancomicina na terapia empírica está associado com o aparecimento de bactérias Gram-positivas e Gram-negativas resistentes. Assim, os hematologistas devem estar cientes do impacto negativo destas práticas na emergência de infecções por bactérias multi-resistentes, uma vez que estas infecções estão associadas a uma alta mortalidade. Rev bras hematol hemoter., 2002, 24(3):220-227

Palavras-chave: Infecção bacteriana, antibiótico, resistência, transplantede medula óssea
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Recebido: 10/06/2002
Aceito: 15/06/2002