CHAPTER 12

Infections after HSCT

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1. Introduction

Infections remain a main cause of morbidity and mortality in patients undergoing HSCT. In recent years, improvement in supportive care measures, better understanding of the mechanism of immunosuppression, the introduction of reduced intensity conditioning (RIC) regimens and new anti-infectious agents and prophylactic strategies have decreased infectious morbidity and mortality; however, there is still room for improvement (1).

The principal risk factors for infections after HSCT are the status of the haematological disease at HSCT, the co-morbidities of the patient, the degree of neutropenia, the disruption of anatomical barriers (mucositis and indwelling catheters), depressed T- and B-cell function and immunosuppressive therapy. The reconstitution of immune status after HSCT depends on the type of transplantation (autologous or allogeneic), the source of progenitor cells (bone marrow, peripheral blood or cord blood), the conditioning regimen (myeloablativive, RIC, or non-myeloablativive), the degree of histocompatibility between the donor and the recipient (sibling, unrelated or mismatch), the type of GvHD prophylaxis (calcineurin or mTOR inhibitors, mono- or polyclonal antibodies or T-cell depletion) and the presence and grade of GvHD and its treatment. Depending on these factors, the patient can be immunodeficient for months or years after HSCT (see Chapter 14). There is a clear relationship between the type of immunodeficiency after HSCT and the incidence of certain infections. According to this, three different periods can be distinguished, with a predominance of specific pathogens in each phase (Figure 1) (2).

2. Chronology of infections after HSCT

2.1 Early or neutropenic phase (days 0 to +30)

This first period spans from conditioning up to engraftment. During this period, all risk factors for infections are present. Although neutropenia and disruption of anatomical barriers (mucosal damage and vascular devices) are the most relevant risk factors in this phase, cellular and humoral immunodefiency and, in patients receiving TBI, functional asplenia are also present. The principal pathogens observed in this phase are Gram-positive and -negative bacteria, Candida spp. and the Herpes simplex virus (HSV) and the most frequent type of infections are bacteraemia/sepsis, pneumonia, oropharingitis, sinusitis, proctitis and cellulitis. The types of infectious complication in this period are the same after autologous and allogeneic HSCT. However, after autologous HSCT, the risk of bacterial infections and their mortality rate are lower due to the usually less intensive mucositis and the shorter neutropenia. In the autologous setting, the infection risk almost completely disappears after neutrophil recovery.
2.2 Intermediate phase (days +30 to +100)

The second phase starts at marrow engraftment. At this time, neutropenia and mucositis have disappeared but central lines, immunodeficiency and functional asplenia, which may be worsened and maintained by GvHD and its treatment, persist. This favours the development of viral and fungal infections. Cytomegalovirus (CMV), adenovirus, BK polyomavirus, respiratory viruses, *Pneumocystis jiroveci* (Pj), *Candida* spp., *Aspergillus* spp. and other moulds are responsible for infections in this phase.

For decades, CMV disease was the principal infectious complication in this phase; however, with the introduction of good surveillance techniques that allow anticipated diagnosis and pre-emptive treatment, the mortality due to CMV has decreased notably (see below) (3). Currently, invasive aspergillosis (IA) is observed in 5–15% of
allogeneic HSCT recipients, 60% of whom will die because of this infection despite the efficacy of the new antifungal agents (4).

2.3 Late post-transplantation phase (days > +100)
Infections occurring during this period are associated with the presence and severity of chronic GvHD, which prevents the normal recovery of cellular and humoral immunity. In addition, functional asplenia persists in patients with GvHD and in those receiving TBI. For this reason, in this phase, infections are generally secondary to encapsulated bacteria (*Streptococcus pneumoniae* and *Haemophilus influenzae*), *Aspergillus* spp. and other moulds, *Pj* and *Varicella zoster virus* (VZV).

In this late phase, a clear relationship exists between the degree of recovery of cellular immunity and infectious complications. Thus, the number of CD4+ cells correlates with certain infections/reactivations (Figure 2). Clear examples of this are the reactivation of *Toxoplasma gondii* in sero-positive patients and the *Pj* pneumonia observed when TMP-SMZ prophylaxis is stopped before CD4+ recovery (2).

![Figure 2: Risk of infection/reactivation depending on CD4+ counts](image)

**2.4 Some considerations about this chronology**
The chronology of infections mentioned previously was described in patients receiving a myeloablative HSCT, but some differences can be observed in recipients of autologous HSCT or RIC-HSCT. Thus, in the autologous setting, as mentioned previously, bacterial infections are less frequent and severe and the other infections mentioned are exceptional. However, patients receiving immunosuppressive agents (steroids, purine analogues or monoclonal antibodies such as rituximab or alemtuzumab) or with severe hypogammaglobulinaemia prior to the auto-HSCT are
at risk of developing infections similar to those observed in the allogeneic setting. In the past decade, RIC-HSCT has been used increasingly worldwide (see Chapter 8). Infections related to neutropenia and mucositis are less frequent with this modality of HSCT than after conventional HSCT. However, viral and fungal infections occurring in the intermediate and late period are comparable because the incidence and severity of GvHD is similar to that observed in myeloablative HSCT. Additionally, RIC-HSCT is usually applied to older patients, who have worse general condition and co-morbidities; for all these reasons, the infection-related mortality has not decreased in this setting (5).

3. **Bacterial infections**

3.1 **Early phase after HSCT (neutropenic phase)**

The main sources of bacterial infections in neutropenic patients are the normal endogenous flora in the gastrointestinal tract, which is responsible for infections by Gram-negative bacteria, and the exogenous acquisition of organisms from vascular devices, which is the main cause of infections by Gram-positive microorganisms. Analysis of catheter-related infections is beyond the scope of this chapter; for those interested, guidelines for the diagnosis and management of intravascular catheter-related infection have been published recently (see reference 6).

Interestingly, only 30–35% of febrile episodes in neutropenic patients can be documented microbiologically; in the remaining cases, the cause of the fever cannot be demonstrated. In the 1990s, Gram-positive bacteria were the pathogens isolated most frequently in cultures; in contrast, since the beginning of the current century, Gram-negative bacteria are re-emerging. Because most of these bacterial infections occur while the patient is treated in hospital, they can have a nosocomial origin; consequently, the epidemiology and protective measures used in the centre acquire special relevance.

3.1.1 **Prophylaxis**

Anti-bacterial prophylaxis has been general practice in this phase of HSCT. It is based on the elimination of endogenous gastrointestinal flora and on the prevention of the acquisition of exogenous organisms. The most important measures are hand-washing, oral hygiene, low-bacterial diets and gastrointestinal decontamination (GID) using oral antibiotics. Hand-washing is the only environmental measure with proven efficacy (level of recommendation AI) and should be used systematically in all cases. In this phase, the use of masks is indicated for all visitors and health care personnel in close contact with the patient, or if they present symptoms of upper
respiratory tract infection and contact with the patients cannot be avoided. The effectiveness of other protective measures (gowns, caps and leggings) has not been proven in this context (7).

The value of a low-bacterial diet has been questioned recently by the results of a randomised trial that compared cooked versus non-cooked food. In that study, cooked food was not associated with any survival advantages (8). Nevertheless, low-bacterial diets continues to be a general and reasonable practice in HSCT units. GID has changed with the years. Up to the 1980s, this prophylaxis was achieved using non-absorbable antibiotics (i.e., gentamicin, vancomycin and nystatin (GVN)) that produced a complete GID; however, because of poor compliance and high cost, it has been generally abandoned. After the introduction by Van der Vaaij of the concept of “resistance to colonisation” (the presence of anaerobic bacteria in the intestine prevents the proliferation and, consequently, hampers the risk of aerobic bacteria translocation), co-trimoxazole (TMP-SMZ) and quinolones were used to destroy intestinal aerobic flora selectively. Because of the haematopoietic toxicity of TMP-SMZ, quinolones have been adopted systematically in HSCT since the 1980s. Many randomised studies and meta-analyses have been published on this topic (9) and the European Conference on Infections in Leukaemia (ECIL) guidelines recommend prophylaxis with fluoroquinolones during all the neutropenic phase for patients with acute leukaemia or for recipients of HSCT, with a strength of recommendation and level of evidence of AI (10).

3.1.2 Diagnosis

In the diagnostic work-up for any immunocompromised patient with fever the following aspects must be analysed systematically:

a. Epidemiological exposures (epidemic outbreaks and contact with children or other patients) and the status of the patient’s microbiological flora (knowledge of previous antibiotics and infections); the possibility of reactivations (history of travelling, positive serologies, past tuberculosis, endemic mycoses, etc.)

b. The predominant type of immunosuppression (neutropenia, mucositis, type of immunodeficiency, function of the spleen, etc.) and

c. The preventive measures used (prophylactic agents, type of isolation and vaccines received).

This information must be completed by obtaining samples from blood, urine, stools and other possible foci of infection for cultures, PCR studies, antigen detection, biochemical analyses (basic and C-reactive protein), blood gases, and imaging techniques (chest-X ray, CT, MRI and ultrasound). As catheter-associated infections are a leading cause of blood-stream infections in this phase, the observation of a
differential growing time greater than 2 hours between cultures obtained simultaneously from catheter and from peripheral blood using automated blood culture systems can be very useful for establishing a correct diagnosis without removing the line (6).

3.1.3 Treatment
In a neutropenic patient with fever, antibiotic treatment should be started immediately, based on an empirical approach and adapted to the flora usually observed in each centre, to the expected flora of the patient and to his/her clinical situation (11). The patient’s flora changes during the time course of treatment and it is not the same after receiving antibiotics for several days or when treated in an ICU as it was during the first febrile episode in the neutropenic phase. Similarly, the approach must be completely different if the patient has an evident focus of infection (e.g., pneumonia, meningitis, abscess or cellulitis) - a situation in which the bacterial burden is high - rather than if a simple bacteraemia or a catheter infection with a low bacterial burden are present. This is why a standard febrile neutropenic patient without a focus of infection can be treated with monotherapy using a beta-lactam antibiotic active against Gram-positive and Gram-negative agents (including *Pseudomonas aeruginosa*), such as piperacillin/tazobactam, carbapenem or cefepime. However, in centres with a high incidence Gram-negative pathogens producing extended-spectrum beta-lactamases, the initial treatment must include a carbapenem (imi-, mero-, or doripenem). In this phase, neither an aminoglycoside nor a glycopeptide are recommended (as they exhibit more toxicity than survival benefit). Similarly, in the case of a persistent fever with negative cultures and absence of focal signs, the addition of a glycopeptide is not recommended (as Gram-positive agents are usually detected in blood cultures and have a low mortality rate). A neutropenic patient with a catheter infection, a severe mucositis or colonisation by MRSA is a completely different scenario; in these cases, a glycopeptide (or one of the new agents as doripenem or linezolid) should be added to the beta-lactam antibiotic (10).

If an infectious focus (e.g., pneumonia, typhlitis or cellulitis) exists, or if the patient has received antibiotics recently, or is colonised with resistant Gram-negative agents, an aminoglycoside must be added to the initial treatment. In the case of neutropenic patients presenting sepsis, shock or worsening after the first days of treatment, a treatment with a beta-lactam antibiotic, aminoglycoside and glycopeptide (or doripenem) should be started promptly (11).

In all cases, it is important to note that fever can persist up to 5–7 days after starting the antibiotic treatment. In this situation, if the patient is in a good clinical condition, there is no need to change the initial treatment. The reduction in the
levels of C-reactive protein and/or procalcitonin can help to confirm that the infection is resolving.

3.2 Late infections
Bacterial infections occurring in this period are generally secondary to encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*) and are favoured by chronic GvHD and its treatment, functional asplenia, hypogammaglobulinaemia and the absence of specific antibodies. Patients receiving total body irradiation (TBI) also have a higher risk of pneumococcal sepsis (12).

3.2.1 Prophylaxis
Measures against encapsulated bacteria are well established: vaccination 6–12 months after HSCT (or when chronic GvHD is controlled) (see Table 1), administration of penicillin (or a macrolide) while under immunosuppressive treatment and immunoglobulin replacement (if severe hypogammaglobulinaemia and repeated infections are observed).

When evaluating an HSCT patient with fever in this late phase, it is necessary to remember that other “rare” bacterial infections produced by *Mycobacterium, Nocardia, Listeria* and *Legionella* are observed occasionally in these patients (2).

### Table 1: Vaccinations recommended after autologous and allogeneic HSCT

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommended after HSCT</th>
<th>Time to vaccine</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal (conjugated)*</td>
<td>Yes (BI)</td>
<td>3–6 months</td>
<td>3*</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Yes (BII)</td>
<td>6–12 months</td>
<td>3</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Yes (BII)</td>
<td>6–12 months</td>
<td>3</td>
</tr>
<tr>
<td>Pertussis (acellular)</td>
<td>Yes (CIII)</td>
<td>6–12 months</td>
<td>3</td>
</tr>
<tr>
<td><em>Haemophilus</em> (conjugated)</td>
<td>Yes (BII)</td>
<td>6–12 months</td>
<td>3</td>
</tr>
<tr>
<td>Meningococcal (conjugate)</td>
<td>National recommendations (BII)</td>
<td>6–12 months</td>
<td>1</td>
</tr>
<tr>
<td>Polio (inactivated)</td>
<td>Yes (BII)</td>
<td>6–12 months</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis B (recombinant)</td>
<td>National recommendations (BII)</td>
<td>6–12 months</td>
<td>3</td>
</tr>
<tr>
<td>Influenza (recombinant)</td>
<td>Yearly (AII)</td>
<td>4–6 months</td>
<td>1–2</td>
</tr>
<tr>
<td>Measles</td>
<td>Yes (BII)</td>
<td>24 months</td>
<td>1–2</td>
</tr>
<tr>
<td>Mumps</td>
<td>Yes (CIII)</td>
<td>24 months</td>
<td>1–2</td>
</tr>
<tr>
<td>Rubella</td>
<td>Yes (BIII)</td>
<td>24 months</td>
<td>1–2</td>
</tr>
</tbody>
</table>

Adapted from (2) and (13). *Followed by 2 doses of polysaccharide vaccine at 12 and 24 m (14)
4. Fungal infections

4.1 Pathogenesis and epidemiology

As mentioned previously, fungal infections also follow a chronological pattern after HSCT (see Figure 1). In the first period, with neutropenia as the main risk factor, infections due to Candida spp. are the most common. The most relevant fungal infections occur in the intermediate/late phase and are favoured by the presence of GvHD and its treatment. Approximately 5–15% of HSCT patients develop invasive aspergillosis (IA) and 60% of them will die because of this, rendering it the main cause of infectious mortality after HSCT (15). Yeasts (with Candida as a representative) are acquired by translocation from intestinal mucosa or through the catheters. In contrast, Aspergillus spp. and other moulds are usually acquired by inhalation of spores (conidia) present in the air, causing rhinosinusitis or pneumonias. Rarely, they can be acquired through the skin, causing onychomycoses or mucosal infections. In normal conditions, the Aspergillus agents reaching the lung via inhalation are phagocytosed by pulmonary macrophages. If these macrophages are non-functional because of cellular immunosuppression or the use of steroids, Aspergillus can grow by germination, producing hyphae. Neutrophils are capable of stopping this growth; however, if neutropenia exists, Aspergillus continues to grow and, because of its angioinvasive capacity, can disseminate and occlude small vessels, producing avascular spaces.

4.2 Prophylaxis

Because mould infections are acquired mainly by inhalation, protective environment measures can be extremely relevant. The use of isolation rooms equipped with HEPA filters (filters that retain 99.97% of air particles with more than 0.3 μm, including bacteria, fungi and even viruses adherent to dust) permit the reduction of the risk of mould acquisition. Several studies have demonstrated their usefulness in reducing Aspergillus in the air and the incidence of IA. Unfortunately, these isolation measures are only applicable when patients are hospitalised, and the risk of infection by moulds lasts for several months after HSCT, when patients are no longer hospitalised (see Figure 1). Only one registry study has shown a survival benefit of HEPA/LAF rooms for patients receiving an allogeneic HSCT for leukaemia (16); however, many other authors have questioned their efficacy (7) or have reported large series of HSCT performed without protective environmental measures with a low incidence of IA (17). The low incidence of conidia in the air of centres situated in geographical areas with a high latitude, frequent rain and cold climate may be an explanation for these differing observations. Despite their theoretical effectiveness,
there is limited experience with the use of portable HEPA filters and FFP3 masks. Regarding pharmacological antifungal prophylaxis, fluconazole has been the gold standard for many years as a consequence of some initial studies showing a survival advantage for auto- and allo-HSCT recipients receiving this prophylaxis. Fluconazole is excellent for most *Candida* spp. and for *Cryptococcus*, but is ineffective against *C. glabrata* and *krusei*, *Aspergillus* and other moulds. Further studies demonstrated that itraconazole may be a good alternative to fluconazole, but its low tolerance and its toxicity hamper its use. Micafungin has an efficacy that is similar to that of fluconazole. Prophylaxis with voriconazole did not yield better survival than that using fluconazole or itraconazole, but decreased the incidence of *Aspergillus* infections (18). Finally, prophylaxis with posaconazole offered a better survival compared with standard azoles in HSCT patients with GvHD (19). Consequently, the ECIL-3 guidelines strongly recommend posaconazole (AI) or voriconazole (for patients who already have a provisional AI) prophylaxis for HSCT patients with GvHD (*Table 2*) (4). Recently, a randomised, placebo-controlled trial has shown the effectiveness of aerosolised liposomal amphotericin B for prophylaxis of invasive pulmonary aspergillosis in neutropenic and HSCT patients (20).

Prophylaxis against *Pneumocystis jiroveci* is a mandatory practice in autologous and allogeneic HSCT, from the beginning of the procedure until CD4+ T-cell counts are above 200–400 x 10⁶/L. The best prophylactic regimen is oral TMP-SMX 2–3 days/week (if administered 3 days/week, the prophylaxis is also effective against *Toxoplasma*). If this drug cannot be administered, aerosolised pentamidine (using a previous bronchodilator and administering half of the dose in the Trendelenburg position), dapsone or atovaquone are good alternatives.

<table>
<thead>
<tr>
<th>Antifungal drug</th>
<th>Initial neutropenic phase</th>
<th>With severe GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole (400 mg/d oral)</td>
<td>AI</td>
<td>CI</td>
</tr>
<tr>
<td>Itraconazole (400 mg/d oral*)</td>
<td>BI</td>
<td>BI</td>
</tr>
<tr>
<td>Voriconazole (400 mg/d oral)</td>
<td>AI (provisional)</td>
<td>AI (provisional)</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Echinocandins (iv)</td>
<td>--</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Micafungin (50 mg/d iv)</td>
<td>CI</td>
<td>--</td>
</tr>
<tr>
<td>Polyenes (iv)</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>Aerosolised L-AmB + fluco oral</td>
<td>BII</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>

*L-AmB: liposomal amphotericin B; *200 mg iv followed by oral solution*
4.3 Diagnosis

The diagnosis of fungal infections is based on histopathology, imaging techniques and microbiology. Histopathology remains the gold standard for diagnosis because it is the proof that there is a fungal infection in a tissue; however, although a description of the fungi can be made, the diagnosis of the species relies on the microbiology.

Microbiology is the hall-mark in the diagnosis of fungal infections. There are several techniques. Direct examination of sputum, BAL and skin samples with different staining often allows diagnosis on the same day. Although they require a few days, cultures (with specific media for moulds and yeasts) lead to the identification of the species of the fungi. The development of serological methods has been the most important advance in this field. Among them, the detection of Aspergillus galactomannan (GM) antigen and beta-D-glucan are the most relevant.

GM detection has become a standard technique in the follow-up of patients at risk of IA. With a cut-off value of 0.5, it permits the detection of IA some days before the classical clinical/radiological manifestations appear (21). The sensitivity of GM decreases under prophylaxis against moulds. Possible false-positive results are another caveat of this test, especially after the ingestion of some foods or when receiving certain antibiotics, such as piperacillin/tazobactam.

Regarding imaging techniques, conventional radiology has many limitations. Although an abnormal chest X-ray is sufficient to suspect the diagnosis, an unremarkable X-ray must be followed by a CT scan. The observation of the so-called halo and crescent signs is compatible with the diagnosis of IA and, recently, the reverse halo sign has also been described as suggestive of zygomycosis. The halo sign appears early in the development of the infection and, after 3 days, most images in CT scans become less specific. This observation stress the relevance of a prompt CT scan to evaluate these patients because the probability of survival improves notably if the treatment is started when the halo sign is observed (22). Biopsy guided by CT scan is a complementary intervention that can allow the diagnosis.

The stratification for investigational purposes of invasive fungal infections as proven, probable and possible using clinical, histopathological, imaging and microbiological data has been a relevant step in this field (see Figure 3) (23).

4.4 Treatment

In recent years, there has been an increasing interest in antifungal treatment because of the introduction of new agents and the development of different therapeutic approaches using confusing terminologies. Empirical antifungal treatment can be defined as antifungal treatment administered to a patient with fever after 5–7 days of anti-bacterial therapy with negative clinical, microbiological and radiological
This strategy was established 30 years ago based on two small studies and became a standard in haematological practice. The main criticism of this approach is that about 70–80% of the patients treated empirically do not have a fungal infection. Several randomised studies were designed to compare the different new agents when used for empirical treatment; all they yielded similar results (see Table 3).

**Figure 3: Main criteria for proven, probable and possible invasive fungal infection**

<table>
<thead>
<tr>
<th>Proven IFI</th>
<th>Probable IF</th>
<th>Possible IF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological</strong></td>
<td>Host factors (neutropenia, immunosuppressants)</td>
<td>Host factors</td>
</tr>
<tr>
<td>or culture evidence</td>
<td>+ Mycological criteria (direct - cytology, culture</td>
<td>+ Clinical criteria</td>
</tr>
<tr>
<td>(in sterile material)</td>
<td>of non sterile material - or indirect tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- GM or βDG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Clinical criteria (+CT/MRI, FBS, retinal)</td>
<td></td>
</tr>
</tbody>
</table>

**GM:** galactomannan; **βDG:** beta-D-glucan; **FBS:** fibrobronchoscopy. **Retinal:** retinal images suggestive of IFI. For complete description of host, clinical and microbiological criteria see reference (22).

results. This strategy was established 30 years ago based on two small studies and became a standard in haematological practice. The main criticism of this approach is that about 70–80% of the patients treated empirically do not have a fungal infection. Several randomised studies were designed to compare the different new agents when used for empirical treatment; all they yielded similar results (see Table 3).

**Table 3: Double-blind clinical trials on empirical antifungal therapy**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Drugs compared</th>
<th>Outcome baseline IFI</th>
<th>Breakthrough IFI</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, 1998</td>
<td>ABCD* vs AmB-d</td>
<td>NS</td>
<td>NS</td>
<td>* Less</td>
</tr>
<tr>
<td>Walsh, 1999</td>
<td>Lipo-AmB* vs AmB-d</td>
<td>NS</td>
<td>* Less</td>
<td>* Less</td>
</tr>
<tr>
<td>Wingard, 2000</td>
<td>ABCD* vs Lipo-AmB</td>
<td>NS</td>
<td>NS</td>
<td>* More</td>
</tr>
<tr>
<td>Walsh, 2002</td>
<td>Vori* vs Lipo-AmB</td>
<td>NS</td>
<td>* Less</td>
<td>NS</td>
</tr>
<tr>
<td>Walsh, 2004</td>
<td>Caspo* vs Lipo-AmB</td>
<td>* Better</td>
<td>NS</td>
<td>* Less</td>
</tr>
</tbody>
</table>

**ABCD:** amphotericin B colloidal dispersion; **Lipo-AmB:** liposomal amphotericin B; **AmB-d:** amphotericin B deoxycholate; **Vori:** voriconazole; **CaspO:** caspofungin; **NS:** no significant difference.

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If using this empirical approach, ECIL-3 guidelines recommend the use of caspofungin or liposomal amphotericin B (degree of recommendation AI) (4). However, because of the improvement of diagnostic techniques, the same ECIL guidelines suggest the transition to an early or anticipated antifungal treatment. The aim of this approach is to start antifungal treatment when the patient is at risk of invasive fungal infection and there is a positive antigen test (GM or beta-D-glucan) or a CT scan that is compatible with a fungal infection (24). Therapeutic strategies based on this approach are clearly effective and markedly reduce the cost of the treatment. Unfortunately, this strategy can only be applied in centres able to perform GM determinations twice a week and a CT scan promptly when requested. Directed antifungal treatment is used to treat patients with a proven diagnosis of fungal infection. Despite the fact that Candida albicans, tropicalis and parapsilosis are sensitive to all antifungals, the guidelines on candidaemia treatment in HSCT recipients recommend the initiation of treatment using a broad spectrum antifungal agent, followed by adjustment of the agent when the Candida species is identified (4). In patients with invasive candidiasis with criteria of severe sepsis, presence of metastasis or focal infection, colonisation by C. krusei or under prophylaxis with fluconazole, the recommendation is to start treatment using a candin, voriconazole or amphotericin B, whereas fluconazole is the drug of choice in the remaining situations. Catheter removal is recommended whenever possible in haematological patients with candidaemia or with C. parapsilosis. Voriconazole is recommended as the first-line treatment for IA and offers a response rate of ~50% (25). For salvage treatment, the global response to the different antifungals is ~40% (Table 4). Although antifungal combinations are not recommended routinely for IA treatment, this approach should be considered in patients with severe sepsis, respiratory failure or CNS involvement; however, at present no randomised study has been performed to support this policy. It is important to remember that, during the first days of treatment of IA, the image of the pulmonary lesion can grow; this represents the normal kinetics of the infection and does not correlate with a poor outcome. The reduction in GM levels confirms a good response to treatment.

5. Viral infections

Viral infections after HSCT also follow a specific chronology (see Figure 1). Limitations of space in this chapter preclude the analysis of all the viruses that can affect HSCT recipients. We summarise the more relevant in the allogeneic setting (CMV, EBV and HHV-6); BK polyomavirus is covered in chapter 11 and the remainder can be consulted in the references attached (2, 3, 27).
5.1 Cytomegalovirus

Around 40–80% of people (depending on the country) are infected by CMV (herpes virus type 5) in childhood. After infection (positive IgM serology), CMV becomes latent for life (positive IgG serology). Under certain circumstances, as in immunosuppression following HSCT, latent CMV can reactivate.

5.1.1 Diagnosis

CMV infection/reactivation can be detected using several techniques (mainly CMV antigenaemia and PCR using blood samples). A positive result indicates an active CMV infection/reactivation. The diagnosis of CMV disease can be established when this infection/reactivation is accompanied by clinical manifestations. There are well-defined criteria for the diagnosis of CMV disease in each of the organs which are commonly affected, e.g., lung, gastrointestinal tract, brain, and eye (28).

5.1.2 Management

For decades, CMV disease was the most important cause of infectious morbidity and mortality after HSCT. The development of good reliable techniques for the diagnosis of CMV infection (antigenaemia and PCR) allows the treatment of the infection/reactivation before the development of CMV disease (pre-emptive or anticipated treatment) (29).

It is very important to prevent infection in patients with a negative CMV IgG serology.
before HSCT. For this purpose, transfusions using filtered products or from seronegative donors are mandatory. These patients have to be trained to avoid sharing cups, glasses and eating tools, to use condoms if not monogamous and to perform regular hand-washing. When possible, a CMV seronegative donor should be chosen because the outcome of HSCT is improved in these cases.

In a patient with a positive CMV IgG serology, there are two possible strategies:

a. Primary prophylaxis: administration of universal prophylaxis using high-dose acyclovir or ganciclovir to all seropositive patients. This is an effective but toxic and non-cost-effective approach that usually is reserved for populations with a very high risk of CMV disease (i.e. cord blood HSCT);

b. Pre-emptive approach: treatment of the infection detected by antigenaemia or PCR before the development of CMV disease using either ganciclovir or foscarnet. This approach is preferred by most teams, but requires the monitoring of CMV twice a week during the period at risk (at least until day +100).

It is important to note that, although the mortality due to CMV has decreased using this strategy, an increase of late CMV disease, which has the same mortality as early disease, has been observed. The median time of appearance of these late cases is around day +180, and patients with low numbers of CD4+ T-cells and with chronic GvHD are at higher risk. The selection of sero-positive donors for sero-positive patients is preferred.

5.1.3 Treatment

Although CMV management has improved the outcome of HSCT, the mortality of CMV disease remains high. Thus, the mortality of CMV pneumonia, which to date has been the most frequent clinical presentation of CMV infection, can increase up to 50–70%. Currently, gastrointestinal CMV disease seems to be more frequent than its pulmonary forms among patients receiving RIC-HSCT. First-line treatment depends on the organ affected:

a. CMV pneumonia: ganciclovir (or foscarnet if a pancytopenia exists) associated with high dose of intravenous immunoglobulin (500 mg/kg every 48 h; seven to 10 doses, followed by a weekly maintenance dose for 2–4 weeks);

b. Other forms of CMV disease: either ganciclovir or foscarnet, without immunoglobulin.

The oral presentation of ganciclovir (valganciclovir) is used extensively but should be used with caution. As a fixed dose is recommended, the monitoring of peripheral counts and renal function is mandatory, especially in patients with low body weight, because of its excellent bioavailability. Second-line treatment is based on cidofovir or the combination of ganciclovir with foscarnet.
5.2 Epstein-Barr virus
Another herpes virus, Epstein-Barr virus (EBV), is associated with post-HSCT lymphoproliferative disease (EBV-PTLD), which is a life-threatening complication. The following risk factors increase the risk of PTLD: unrelated and/or mismatched HSCT; use of T-cell depletion, ATG or OKT3; EBV serology mismatch between the donor and the recipient (increased risk for sero-negative patients with a sero-positive donor); primary EBV infection and splenectomy. Monitoring of EBV reactivation using quantitative PCR (at least once a week for 3 months) is recommended for this high-risk population to allow pre-emptive treatment if a rise in viral load is observed. The ECIL-2 recommendations for pre-emptive treatment are: rituximab (375 mg/m², one or two doses), reduction of immunosuppression, when possible, and donor EBV-specific cytotoxic T-lymphocytes, if available. Antiviral drugs are not recommended. In cases of established EBV-PTLD, the same measures must be applied; if there is no response, donor lymphocyte infusions or chemotherapy are additional options (24).

5.3 Human herpes virus 6
Human herpes virus 6 (HHV-6) in the setting of allogeneic HSCT reactivates in 50–70% of patients (typically earlier than CMV) and has distinctive clinical manifestations that can help its diagnosis: encephalitis, with characteristic limbic- and hippocampus-derived symptoms, can be confirmed using MRI studies, EEG changes and demonstration of the presence of HHV-6 DNA in the CNS; marrow suppression is observed as a delayed engraftment or graft failure together with positive HHV-6 PCR in blood; and skin rash, which is predominant in cheeks and resembles an acute GvHD, is also characteristic. Any of these symptoms/signs is suspicious of HHV-6 reactivation. Treatment consists of either foscarnet or ganciclovir (30).

References


19. Ullmann AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in


Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/online-training/handbook/

1. Regarding the chronology of infections after HSCT, which of the following is not a risk factor in the early or neutropenic phase?
   a) Neutropenia
   b) Disruption of anatomical barriers

HAEMATOPOIETIC STEM CELL TRANSPLANTATION
c) Cellular and humoral immunodeficiency

d) Chronic GvHD

2. In the late post-transplantation phase, which of the following agents is not a frequent cause of infection?
   a) Candida
   b) Varicella zoster virus
   c) Aspergillus
   d) Haemophilus influenzae

3. Which of the following statements is false?
   a) The main sources of bacterial infections in neutropenic patients are the normal endogenous flora in the gastrointestinal tract.
   b) Vascular devices are not associated with infections by Gram-positive microorganisms.
   c) Only 30–35% of febrile episodes in neutropenic patients can be documented.
   d) Most of the bacterial infections can have a nosocomial origin.

4. In a neutropenic patient with fever, which of the following statements is false?
   a) Treatment should be started immediately.
   b) Treatment should be adapted to the flora of each hospital.
   c) It is not important to start antibiotics immediately, wait until the results of cultures.
   d) A neutropenic patient without an infectious focus can be treated with monotherapy.

5. In a case of invasive aspergillosis, which of the following antifungal agents is not effective?
   a) Fluconazole
   b) Voriconazole
   c) Candins
   d) Amphotericin B