Invasive Fungal Infections

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37.1 Epidemiology

Invasive fungal diseases (IFD) are frequent infectious complications of HSCT. The 12 m cumulative incidence approaches 8–10% in URD or mismatched allo-HSCT, 6% in MRD allo-HSCT, and less than 2% following auto-HSCT (Kontoyiannis et al. 2010). However, higher incidences (up to 17%) have been reported in haploidentical HSCT and CBT.

Classical risk periods for IFD include (a) the pre-engraftment period when neutropenia and mucosal damage are most profound, (b) the early post-engraftment period (days +40 to +100) when patients are at highest risk for acute GvHD and viral reactivations due to defective T-cell immunity, and (c) the late post-engraftment period (beyond day +100) complicated by chronic GvHD, delayed immune reconstitution, and occasionally secondary neutropenia. The Gruppo Italiano Trapianto Midollo Osseo (GITMO) has identified period-specific risk factors for proven and probable IFD (Girmenia et al. 2014). The presence of a proven or probable IFD is an independent and strong negative predictor of overall mortality at 1 year after allogeneic HSCT.

Before the introduction of antifungal prophylaxis, *Candida* infections were prevalent in as many as 18–20% of HSCT recipients. However, the widespread use of fluconazole prophylaxis since the late 1990s has significantly reduced the incidence of systemic *Candida* infections and has decreased the transplant-related mortality secondary to *Candida* infections and to gut GvHD. But, this successful approach has also resulted in an epidemiological shift from fluconazole-susceptible *Candida albicans* infections to predominantly fluconazole-resistant non-*albicans Candida* infections (including *Candida glabrata* and *Candida krusei*). Based on a recent EBMT study, the incidence of candidemia by day +100 has now dropped to 1.2% but remains associated with increased NRM and lower short- and long-term OS (with candidemia being an independent risk factor for NRM and OS) (Cesaro et al. 2018).

Over the past two decades, respiratory mould infections caused by *Aspergillus* species (and to a much lesser extent non-*Aspergillus* moulds such as *Mucorales*, *Fusarium* species, and some rare other pathogens) have become much more prevalent. Unlike yeasts, which are acquired through indwelling lines or via intestinal translocation, mould infections are usually acquired by inhalation of airborne spores. In HSCT recipients, the primary lines of defence, including phagocytosing alveolar macrophages and neutrophils, are often nonfunctional in the presence of IS drugs and/or corticosteroids. Hence, *Aspergillus* spores

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E. Carreras et al. (eds.), *The EBMT Handbook*, https://doi.org/10.1007/978-3-030-02278-5_37

may germinate and produce hyphae, which then invade blood vessels, followed by vascular occlusion and infarction and dissemination to distant organs. The crude mortality rate of invasive mould disease in HSCT recipients can be as high as 60%.

37.2 Diagnosis of Fungal Disease

37.2.1 Mould Infections

Despite a high index of clinical suspicion, diagnosing invasive mould disease remains challenging. The clinical presentation in HSCT patients is often nonspecific and difficult to distinguish from non-fungal infections and even noninfectious complications. A diagnosis of mould disease is based on histopathological examination of infected tissue, imaging (in particular chest CT scan) and microbiological tests, both culture based and non-culture based.

Although *histopathology* remains the gold standard for making a definite diagnosis, many clinicians are reluctant to ask for invasive procedures with biopsy in these vulnerable patients with underlying coagulation problems. As a result, the majority of invasive mould diseases are categorised as probable or even possible.

Culture and direct microscopic examination of sputum, BAL and other body fluids, and skin samples, using staining techniques that allow diagnosis on the same day (e.g. optical brighteners such as calcofluor white), have been the cornerstones for making a microbiological diagnosis of invasive mould disease. Culture has the additional advantage of allowing fungal species identification and determining antifungal susceptibility. Unfortunately, culture is time-consuming and requires considerable expertise. In addition, blood cultures are notoriously negative for moulds, even in disseminated disease, and culture from any respiratory specimen has only low to moderate sensitivity and predictive value.

The (ongoing) development of serological tests has been a major advance in the field (Maertens et al. 2016a, b). *Galactomannan* (GM), a fungal cell wall molecule that is released during fungal growth, can be detected by a commercial enzyme immunoassay (Bio-Rad Platelia™ Aspergillus EIA). Earlier studies used an index of ≥1.5 to define positivity. The ECIL guidelines now support the use of a single serum or plasma value of ≥0.7 or multiple (consecutive) values of ≥0.5 to define positivity. This lower cutoff permits detection of fungal infection before the clinico-radiological manifestations appear. However, improved sensitivity with the use of lower cutoffs comes with a loss of specificity. In addition, false-positive results as well as false-negative results are not uncommon (Table 37.1) and cross-reactivity with non-*Aspergillus* moulds (including but not limited to *Fusarium* spp., *Penicillium* spp., *Acremonium* spp., *Alternaria* spp., and *Histoplasma capsulatum*) may occur, although the assay does not detect *Mucorales*. GM testing can also be applied to other types of specimens, including BAL fluid. Cutoff values of 1.0 have been recommended although it is likely that higher thresholds are needed. Recently, an index cutoff of 1.0 has also been suggested for analysing cerebrospinal fluid samples from patients with (suspected) cerebral aspergillosis.

Unlike GM, *β*-d-*glucan* (BDG) is a component of the cell wall of many pathogenic fungi including *Candida* spp., *Fusarium* spp., and *Pneumocystis* (Maertens et al. 2016a, b). The main exceptions are *Mucorales* and some *Cryptococcus* species. The Fungitell® assay (Associates of Cape Cod) has been approved by the US FDA and carries the European CE label for the presumptive diagnosis of invasive fungal infection. Most studies report good sensitivity, but specificity and positive predictive value are poor due to a high rate of false-positive results (Table 37.1), regardless of the specimen. However, the negative predictive value is around 80–90%.

PCR-based methods have also been developed. Lack of standardisation has for a long time hampered the acceptance of these diagnostic assays. Fortunately, over the past decade, the

Table 37.1 Limitations of antigen assays in the diagnosis of invasive fungal disease

	Galactomannan	β-D-glucan
Reactivity with fungal species	*Aspergillus* spp., *Fusarium* spp., *Paecilomyces* spp., *Acremonium* spp., *Penicillium* spp., *Alternaria* spp., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Emmonsia* spp., *Wangiella dermatitidis*, *Prototheca*, *Myceliophthora*, *Geotrichum capitatum*, *Chaetomium globosum*	*Pneumocystis jirovecii*, *Aspergillus* spp., *Fusarium* spp., *Histoplasma capsulatum*, *Candida* spp., *Acremonium* spp., *Trichosporon* sp., *Sporothrix schenckii*, *Saccharomyces cerevisiae*, *Coccidioides immitis*, *Prototheca*
False-positive test results	– Semi-synthetic β-lactam ATB[a] – Multiple myeloma – Blood products collected using Fresenius Kabi bags – Gluconate-containing plasma expanders – Flavoured ice pops/frozen desserts containing sodium gluconate – *Bifidobacterium* spp. (gut) – Severe mucositis or GI GvHD – Enteral nutritional supplements	– Semi-synthetic β-lactam antibiotics – Human blood products, including IVIg, albumin, plasma, coagulation factor infusions, filtered through cellulose membranes – Cellulose haemodialysis/haemofiltration membranes – Exposure to (surgical) gauze – Bacterial bloodstream infections (e.g. *P. aeruginosa)*
False-negative test results	– Concomitant use of mould-active antifungal agents – Mucolytic agents	– Concomitant use of antifungal agents

[a]Including ampicillin, amoxicillin clavulanate, and piperacillin/tazobactam (although this problem seems largely abated compared with previous experience)

European Aspergillus PCR Initiative (EAPCRI) has made tremendous progress in standardising protocols for efficient DNA extraction and amplification (White et al. 2015). Recently a lateral-flow device (LFD) was developed for the point-of-care diagnosis of invasive aspergillosis (Hoenigl et al. 2018); clinical validation studies are currently ongoing.

The sensitivity and specificity of conventional *radiology* are too low to diagnose or to exclude a fungal infection. Thin-section multislice CT scan nowadays is the preferred imaging technique; more recently, computed tomography pulmonary angiography is rapidly gaining popularity as an alternative diagnostic technique (Stanzani et al. 2015). Nodules, with or without a halo sign, are suggestive of invasive mould disease; this 'halo sign' appears early in the course of the infection; thereafter the lesions become more nonspecific. Following neutrophil recovery, an air crescent sign may develop, usually associated with a good outcome. An inversed halo sign has been described as more suggestive of invasive mucormycosis. The added value of PET scan is currently being investigated.

37.2.2 Yeast Infections

Cryptococcal Ag assays have become very sensitive and should be used where cryptococcal meningitis is suspected.

Microbiologic cultures, the gold standard diagnostic method for invasive *Candida* infections and candidemia, have low sensitivity (especially for chronic disseminated candidiasis) and take up to 2–5 days to grow (from blood samples). The T2Candida panel is a novel, fully automated qualitative diagnostic platform for diagnosis of candidemia in whole blood specimens with a mean time to species identification of less than 5 h. The negative predictive value is almost 100% in a population with 5–10% prevalence of candidemia (Mylonakis et al. 2015). Unfortunately, the assay detects only five different *Candida* species.

37.2.3 *Pneumocystis jirovecii* Pneumonia (PJP)

Immunofluorescence assays remain recommended as the most sensitive microscopic

method. Real-time PCR on BAL fluid can be used to rule out the diagnosis of PJP. However, a positive PCR test does not necessarily mean that the patient has PJP, since low fungal loads will be picked up in colonised patients. BDG positivity in serum can further contribute to the diagnosis, although a positive test result may also indicate other fungal infections (Alanio et al. 2016).

37.3 Prevention and Prophylaxis

37.3.1 Protective Environment Measures

Protective environment measures (such as the use of HEPA-filtered isolation rooms or the use of portable HEPA filters) are useful to prevent in-hospital acquisition of airborne fungal pathogens. However, many patients develop IFD during the outpatient follow-up period, when these isolation measures are not applicable.

37.3.2 Pharmacological Antifungal Prophylaxis

Pharmacological antifungal prophylaxis; updated ECIL recommendations are phase-specific (ECIL-5 2013).

37.3.2.1 During the (Neutropenic) Pre-engraftment Phase

Fluconazole (400 mg/day) is still recommended for centres with a low incidence of mould infections [i.e. below 5%] but only when combined with a mould-directed diagnostic approach (biomarker and/or CT scan based) or a mould-directed therapeutic approach (empirical antifungal therapy). Centres with a higher incidence of mould infections are advised to adopt an alternative approach.

Voriconazole (400 mg/day following loading) failed to show a difference in fungal-free survival, overall survival, incidence of IFD, invasive aspergillosis, empirical use of antifungals, and toxicity compared with fluconazole. When tested against itraconazole oral solution, voriconazole was superior for the composite endpoint, but the difference was driven by a lower use of systemic antifungals with voriconazole, which could be given for a longer duration than itraconazole, not by better efficacy. Itraconazole (200 mg IV q24h, followed by oral solution 200 mg q12) provided better protection against invasive mould infections than fluconazole. However, drug toxicities and tolerability limited its usefulness as prophylactic agent. Therefore, voriconazole and itraconazole were both given a B-I recommendation.

Data for the echinocandins are limited to micafungin (50 mg IV q24h). The study comparing micafungin versus fluconazole had significant shortcomings, including the overrepresentation of a low-risk population and the lack of a predefined workup for diagnosing IFD. Hence, prophylaxis with micafungin received a B-I recommendation for centres with a low incidence of mould infections and C-I for those with a high incidence.

The addition of aerosolised liposomal amphotericin B (AmB) to fluconazole is not recommended for centres with a low incidence of mould infections, although there is some evidence to do so in higher-risk centres (B-II). IV liposomal AmB for prophylaxis was given a C-II recommendation.

Although there are no specific studies of posaconazole prophylaxis during the pre-engraftment phase, the drug (oral solution 200 mg q8h or gastro-resistant tablet/IV formulation 300 mg q24h following a loading dose of 300 mg q12h on the first day) was given a B-II recommendation based on results inferred from data during the neutropenic phase in AML/MDS patients.

37.3.2.2 During the (GvHD) Post-engraftment Phase

Given the significantly increased risk of invasive mould infection during GvHD (and its associated high mortality), ECIL strongly recommends against the use of fluconazole for prophylaxis in patients with high-risk GvHD. Based on the results of a large, double-blind study, posaconazole (oral solution or gastro-resistant tablet/IV formulation) is the drug of choice for antifungal

prophylaxis (AI), although no difference was observed in patients with chronic GvHD.

37.3.2.3 PJP Prophylaxis

Oral TMP/SMX given 2–3 times weekly is the drug of choice for the primary prophylaxis of PJP and should be given during the entire period at risk (from engraftment to ≥6 months and as long as IS is ongoing). All other drugs, including aerosolised or IV pentamidine, atovaquone, and dapsone, are considered second-line alternatives when TMP/SMX is poorly tolerated or contraindicated (Maertens et al. 2016a).

37.4 Treatment of Fungal Disease

Over the last few decades, three basic strategies (apart from prophylaxis) have been developed and investigated in clinical studies to deal with IFD (Mercier and Maertens 2017). For a long time, profound and prolonged neutropenia accompanied by persistent or relapsing fever after 5–7 days of adequate antibacterial coverage has been regarded as a sufficient trigger for starting broad-spectrum antifungals, a strategy referred to as *empirical* antifungal therapy. This practice has never been supported by robust scientific evidence and has important drawbacks, including drug-related toxicity and increased cost due to overtreatment. In spite of this, the empirical use of antifungals became standard of care in many centres. It was also endorsed by consensus guidelines and is relied on by centres that have limited or no access to radiological and mycological diagnostic tools. If relying on this approach, ECIL guidelines recommend the use of caspofungin (50 mg/day following 70 mg on day 1) or liposomal amphotericin B at 3 mg/kg (both have an AI recommendation).

A *diagnostic-driven* approach (also called *pre-emptive*) has been advocated by some centres and guidelines following recent improvements in diagnostic techniques. The aim is to start antifungal therapy in at-risk patients only when they present with an early marker of fungal infections, such as a positive GM, BDG, or PCR screening assay, or a suggestive lesion on imaging. Unfortunately, such a strategy is restricted to centres that perform non-culture-based testing twice weekly and readily have access to chest CT scan and other imaging modalities.

Directed antifungal treatment is used for patients with documented fungal disease, either proven or probable (Table 37.2).

- Voriconazole and isavuconazole are recommended as the first-line treatment for invasive aspergillosis, including cerebral aspergillosis (Tissot et al. 2017). In a randomised clinical trial, voriconazole and isavuconazole had the same efficacy (all-cause mortality at day 42 around 20%), although isavuconazole has a better toxicity profile (including hepatotoxicity) and somewhat fewer drug-drug interactions compared to voriconazole (Maertens et al. 2016c). The upfront combination of antifungals with different mechanisms of action (e.g. an azole plus an echinocandin) is not recommended because superiority over monotherapy could not be demonstrated in a recent trial (Marr et al. 2015). Liposomal AMB at 3 mg/kg is the recommended alternative for primary therapy if these azoles cannot be used due to intolerance, drug interactions, prior exposure to broad-spectrum azoles (e.g. prophylaxis), or documented azole resistance (Resendiz Sharpe et al. 2018), an emerging problem in some European centres. For salvage therapy, the global response is around 40%, irrespective of the antifungal used. Treatment duration is typically between 6 and 12 weeks, followed by secondary prophylaxis in patients with ongoing IS therapy. During the first week of treatment, pulmonary lesions can grow on imaging; this is in line with the normal kinetics of the disease and does not correlate with a poor outcome. When elevated at baseline, reduction in serum GM correlates with treatment response.
- Treatment of mucormycosis includes control of the underlying condition, surgical debridement (often destructive), and antifungal therapy. At present, lipid-based formulations of AmB (at doses of 5–10 mg/kg) are the first-line therapy of choice (Tissot et al. 2017; Cornely et al.

Table 37.2 ECIL-6 guidelines for the *first-line antifungal treatment* of IA and mucormycosis in HSCT patients

	Grade	Comments
Invasive aspergillosis		
Voriconazole	AI	Daily adult dose 2 × 6 mg/kg on day 1 followed by 2 × 4 mg/kg (initiation oral therapy: CIII) Need for therapeutic drug monitoring Check for drug-drug interactions
Isavuconazole	AI	Adult dose 200 mg t.i.d. for 2 days, thereafter 200 mg daily As effective as voriconazole but better tolerated
Liposomal amphotericin B	BI	Daily adult dose, 3 mg/kg
Amphotericin B lipid complex	BII	Daily adult dose, 5 mg/kg
Amphotericin B colloidal dispersion	CI	Not more effective than AmB deoxycholate but less nephrotoxic
Caspofungin	CII	
Itraconazole	CIII	
Combination anidulafungin + voriconazole	CI	
Other combinations	CIII	
Recommendation against the use of amphotericin B deoxycholate	AI	Less effective and more toxic
Invasive mucormycosis[a]		
Amphotericin B deoxycholate	CII	
Liposomal amphotericin B	BII	Daily adult dose, 5 mg/kg. Liposomal AmB should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	BII	
Amphotericin B colloidal dispersion	CII	
Posaconazole	CIII	No data to support its use as first-line treatment
Combination therapy	CIII	

[a]Management of mucormycosis includes antifungal therapy, surgery, and control of the underlying condition

2014). Both posaconazole and isavuconazole can be used for oral outpatient therapy following initial stabilisation of the disease.

- Hyalohyphomycosis constitutes a heterogeneous group of fungi, including (but not limited to) *Fusarium*, *Scedosporium*, *Acremonium*, and *Scopulariopsis* species. Clinical manifestations range from colonisation to localised infections to acute invasive and/or disseminated disease. First-line therapy of fusariosis should include voriconazole and surgical debridement where possible; posaconazole can be used as salvage treatment. Voriconazole is also the recommended the first-line treatment of *Scedosporium* infections (except for *Lomentospora prolificans*, previously named *S. prolificans*, for which there is no standard treatment available). The optimal antifungal treatment has not been established for *Acremonium* spp., *Scopulariopsis* spp., and other hyalohyphomycosis (Tortorano et al. 2014).
- Echinocandins are the drugs of choice for the first-line therapy of invasive candidiasis/candidemia, followed by a step-down approach in clinically stable patients upon receipt of the species identification and antifungal susceptibility testing results (Andes et al. 2012). Catheter removal is strongly recommended in patients with candidemia or with *C. parapsilosis* bloodstream infection. Treatment duration typically is 14 days after the last positive blood culture. Of note, echinocandin resistance is on the rise (particularly for *C. glabrata*), and recent outbreaks of multiresistant *C. auris* infections have been reported (Lamoth and Kontoyiannis 2018).
- High-dose trimethoprim/sulfamethoxazole is the treatment of choice for patients with documented PJP; the combination of primaquine plus clindamycin is the preferred alternative. Treatment duration typically is 3 weeks, and secondary anti-PJP prophylaxis

is indicated thereafter. The administration of glucocorticoids must be decided on a case-by-case basis (Maschmeyer et al. 2016).

- Of note, uncertainty about exposure and drug interactions is common when using azole antifungals. Therapeutic drug monitoring for voriconazole (plasma target 1–6 mg/L for prophylaxis and treatment) and posaconazole (plasma target >0.7 mg/L for prophylaxis; >1 mg/L for treatment) is therefore recommended (ECIL-6 guidelines).

Key Points

- *Aspergillus*, *Candida,* and *Pneumocystis jirovecii* are the cause of almost 90% of the invasive fungal diseases following HSCT. Most infections are diagnosed post-engraftment during episodes of acute and/or chronic GvHD.
- Chest and sinus CT scan and non-invasive mycological tools (serology, PCR) are crucial for making an early diagnosis.
- Antifungal prophylaxis, targeting yeast and/or mould infections depending on the post transplant risk period, is highly recommended. TMP/SMX remains the drug of choice for preventing PJP.
- Echinocandins are the preferred first-line therapy for invasive *Candida* infections and candidemia. Voriconazole or isavuconazole is the recommended first-line options for invasive aspergillosis, whereas lipid-based formulations of AmB are the recommended first-line option for mucormycosis.

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