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Liposomal amphotericin B—the present

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Most invasive fungal infections are opportunistic in nature but the epidemiology is constantly changing, with new risk groups being identified. Neutropenia is a classical risk factor for fungal infections, while critically ill patients in the ICU are now increasingly at risk of yeast and mould infections. Factors to be considered when choosing antifungal treatment include the emergence of rarer fungal pathogens, the risk of resistance to azoles and echinocandins and the possibility of drug–drug interactions. Liposomal amphotericin B has retained its place in the therapeutic armamentarium based on its clinical profile: a broad spectrum of antifungal activity with a low risk of resistance, predictable pharmacokinetics with a rapid accumulation at the infection site (including biofilms), a low potential for drug–drug interactions and a low risk of acute and chronic treatment-limiting toxicities versus other formulations of amphotericin B. It is a suitable choice for the first-line empirical or pre-emptive treatment of suspected fungal infections in neutropenic haematology patients and is an excellent alternative for patients with documented fungal disease who can no longer tolerate or continue their first-line azole or echinocandin therapy, both in the haematology setting and in the ICU. Moreover, it is the first-line drug of choice for the treatment of invasive mucormycosis. Finally, liposomal amphotericin B is one of the few antifungal agents approved for use in children of all ages over 1 month and is included in paediatric-specific guidelines for the management of fungal disease.

Introduction

The epidemiology of invasive fungal infections (IFIs) and the number of patients at risk are constantly changing due to advances in medicine and surgery. In European and North American healthcare facilities, candidaemia and invasive candidiasis remain the most frequent invasive mycoses, followed by invasive mould diseases (mainly caused by *Aspergillus* spp. and *Mucorales* spp.), whereas cryptococcal disease and rare mould infections (e.g. *Scedosporium* spp.) seem to be less of a problem. However, there are considerable epidemiological variations between countries and between institutions within the same country due to differences in medical practices (e.g. use of prophylaxis, availability of diagnostic tests, variation in patient population).

Nevertheless, nearly all IFIs are opportunistic in nature; they occur only in individuals with a significant inherited or acquired defect in their innate or adaptive immune system and/or in patients who are hospitalized for a severe underlying disease. Cryptococcosis is especially prevalent in people infected with HIV and with low CD4 counts. Among the patients most susceptible to invasive *Candida* infections are low-birth-weight premature infants (with immunological immaturity), elderly people experiencing immunosenescence, patients undergoing major (often complicated) abdominal surgery with microbial translocation, those with severe pancreatitis, those who have experienced extensive burns or polytrauma, patients with neutropenia and patients with a prolonged stay in an ICU (associated with indwelling lines and intravascular devices, multiple broad-spectrum antibiotic use and total parenteral nutrition, renal replacement therapy and mechanical ventilation, and colonization with the offending *Candida* spp. at various body sites). Risk groups for mould infections (mainly *Aspergillus* spp.) are summarized in Table 1.

For many of these diseases, treatment options with the current antifungal armamentarium are limited and consist of polyenes, azoles and echinocandins. Although the various generations of azoles have been truly game-changing for the field of medical mycology, not least because of their oral as well as parenteral availability, recent years have also witnessed critical shortcomings of these azoles (particularly the mould-active ones): unpredictable exposure due to non-linear pharmacokinetics necessitating therapeutic drug monitoring,[1] acute and chronic treatment-limiting toxicities (e.g. fluoride excess and periostitis, neuropathy, phototoxic reactions, skin cancer) and compliance issues (e.g. food effects).[2] In addition,

Table 1. Characteristics of patients at risk of developing invasive mould infections in contemporary clinical practice

• Prolonged (>10 days) and profound (<500 neutrophils/mm^3) neutropenia, especially following remission induction or reinduction treatment of AML and conditioning treatment to prepare for an allogeneic HSCT
• Graft-versus-host disease treated with immunosuppressive drugs (especially corticosteroids or combination therapy)
• Chronic granulomatous disease; other inherited immunodeficiencies (e.g. CARD9 deficiency)
• Solid organ transplantation: lung > heart > liver > kidney
• Prolonged use of corticosteroids (prednisone or equivalent for >3 weeks at a mean minimum dosage of 0.3 mg/kg/day)
• Treatment with T cell immunosuppressants (e.g. calcineurin inhibitors, alemtuzumab, TNF-α blockers, nucleoside analogues, ibrutinib etc.) during the past 3 months
• Chronic respiratory disease (e.g. COPD, cystic fibrosis), especially while receiving chronic corticosteroid therapy
• Decompensated liver cirrhosis
• Influenza A/B infection requiring ICU admission
• SARS-CoV-2 infection with respiratory failure
• Uncontrolled HIV/AIDS
• Diabetic ketoacidosis (for mucormycosis)

hazardous interactions with essential drugs with a narrow therapeutic window (such as targeted therapies with midostaurin, ibrutinib and venetoclax) have created real dilemmas for treating physicians.[3,4] Finally, triazole resistance, either after prolonged triazole antifungal therapy or after exposure to triazole-resistant conidia from the environment, is being reported increasingly in *Aspergillus fumigatus*.[5] Infections with triazole-resistant *A. fumigatus* have been associated with therapeutic failure and increased mortality.[6] In many of the above-mentioned instances, echinocandins are not a suitable antifungal alternative given their limited spectrum of activity and suboptimal and fungistatic activity against *Aspergillus* spp.[7]

Liposomal amphotericin B (AmBisome®) is a lipid-based formulation of amphotericin B with a much more favourable tolerability and toxicity profile than conventional amphotericin B deoxycholate. Liposomal amphotericin B has a broad spectrum of activity with a low risk of resistance and displays fungicidal activity; further, clinically relevant drug–drug interactions are not expected. The parenteral-only route of administration is a limitation for some patients, although not for critically ill patients, as well as some of the acute infusion-related toxicities and the low risk of moderate-to-severe nephrotoxicity.[8] Given these characteristics, liposomal amphotericin B is currently recommended as the alternative drug of choice for the first-line therapy of invasive aspergillosis,[8,9] the drug of choice for the primary treatment of invasive mucormycosis (including cerebral disease)[9,10] and one of the preferred drugs of choice for the empirical treatment of persistent febrile neutropenia.[9,11] Liposomal amphotericin B is also approved for the treatment of cryptococcal meningitis.[12]

Liposomal amphotericin B in patients with haematological malignancies

The management of IFIs in patients with haematological malignancies remains challenging because of the difficulties in both diagnosis and treatment. Invasive aspergillosis (IA) is the most frequent IFI in this subset of patients and is characterized by high morbidity and mortality. IA occurs mainly in patients who experience prolonged neutropenia following intensive induction chemotherapy, typically for AML and ALL, and those who undergo an allogeneic HSCT.[13–15]

Invasive aspergillosis

Various parameters influence the risk of IA in patients with haematological malignancies, not only neutropenia, which remains the most important factor, but also comorbidities, age, lifestyle, type of transplant, the degree of compatibility between the donor and the patient and particularly the type of chemotherapy for the underlying malignancy.[15]

The treatment of aspergillosis, and IFIs in general, in these patients has been the subject of numerous studies to identify the most effective drugs. Conventional amphotericin B deoxycholate was initially the only drug available for treatment of IA and was considered the drug of choice for many years; however, it no longer has a role where effective and less toxic options are available. Lipid formulations of amphotericin B (i.e. liposomal amphotericin B and amphotericin B lipid complex) were developed to address infusion-related adverse events and nephrotoxicity, while retaining the broad spectrum of activity, and these are now considered more appropriate options.[16,17]

More recently, mould-active triazoles have been introduced. Based on the results of a trial comparing it with conventional amphotericin B deoxycholate, voriconazole became the antifungal agent of choice for first-line therapy of IA.[18] A subsequent comparative trial showed that isavuconazole was non-inferior to voriconazole for the primary treatment of IA and other invasive mould infections and caused fewer drug-related adverse events.[19] More recently, a randomized controlled trial compared posaconazole with voriconazole and demonstrated that

posaconazole was non-inferior to voriconazole for all-cause mortality until Day 42 in participants with IA.[20]

Several guidelines have been compiled, based on review of the literature, to standardize the management of IFIs, particularly IA, including those of the European Conference on Infections in Leukaemia (ECIL), IDSA and ESCMID.[9,11,21] All guidelines have specific recommendations for patients with neutropenia. These guidelines currently recommend voriconazole and isavuconazole as the drugs of choice for the treatment of IA in patients with haematological malignancies, with the same grade of recommendation (voriconazole has a slightly higher recommendation than isavuconazole in the IDSA guidelines). All the international guidelines specify liposomal amphotericin B as a good alternative, although the level of recommendation is lower because of the nephrotoxicity associated with amphotericin B deoxycholate. The level of recommendation is also lower for all other second-generation azoles, echinocandins and other lipid formulations of amphotericin B, based on their efficacy and toxicity.

To date, evidence for the use of antifungal combinations to treat IA comes from limited numbers of patients in case reports and small single-centre studies, and is rather inconclusive. The only prospective randomized study, published in 2015, compared the voriconazole plus anidulafungin combination versus voriconazole. However, limitations in power precluded definitive conclusions about superiority of the combination;[22] hence, current guidelines provide only marginal support for first-line combination therapy. Nevertheless, the combination antifungal approach has been evaluated in the setting of azole-resistant *Aspergillus*.[23,24] This has involved either sequential therapy in which a second antifungal agent is added because of the low or unsatisfactory efficacy of the first drug, or combination therapy from the start with two or even three drugs. Combination antifungal therapy may potentially increase the activity or broaden the spectrum, lessen the risk of resistance and allow a shorter treatment period.

However, some benefits have been observed with combinations compared with individual drug monotherapy.[25,26] An observational study evaluated the feasibility, toxicity and efficacy of an antifungal combination strategy in 84 patients with haematological malignancies. Combination therapy was used from the start in 45 patients and the sequential approach in 39 patients. The most frequently used combinations were caspofungin plus voriconazole (42%), caspofungin plus liposomal amphotericin B (24%) and liposomal amphotericin B plus voriconazole (18%). The combinations were effective and well tolerated, with an overall response rate of 73% (61/84) and no significant differences between regimens; the IFI-related mortality rate was 17%.[26]

Mucormycosis

The treatment of mucormycosis in patients with haematological malignancies typically involves surgical resection of infected tissue and antifungal therapy with liposomal amphotericin B, as well as control of underlying factors predisposing to infection, including correction of neutropenia and discontinuation or reduction of steroids and other immunosuppressive treatments.[27] The efficacy of liposomal amphotericin B has been evaluated in many studies but, due to the rarity of mucormycosis, there have not been randomized clinical trials and the number of patients has been limited. Guidelines recommend liposomal amphotericin B as the drug of choice, with a higher level of evidence than alternative treatments.[10,28] For example, liposomal amphotericin B at a dose of 5 mg/kg/day was associated with a better response rate and survival rate than alternative treatments.[10,28] In addition, 40 patients with mucormycosis were treated with liposomal amphotericin B 10 mg/kg for 1 month (plus surgery when appropriate) in a prospective multicentre study. The overall response rate was 45%, with a 62% survival rate at 12 weeks, but 40% of the patients developed renal impairment (defined as doubling of serum creatinine).[29]

Recent studies have documented the efficacy and safety of isavuconazole and posaconazole in the treatment of mucormycosis, which has led to their use as suitable drugs for this infection even though the registration trials recruited relatively few patients.[30,31]

Considering the aggressiveness of mucormycosis and the high mortality rate, combinations of antifungal drugs, typically a lipid formulation of amphotericin B plus posaconazole, have been evaluated. In a series of 32 cases from two registries, clinical improvement was observed in 56% of patients and 28% died of progressive mucormycosis.[32]

Empirical and pre-emptive therapy

Multiple studies have investigated the empirical and pre-emptive use of liposomal amphotericin B in patients with haematological malignancies undergoing chemotherapy or allogeneic HSCT. An open-label randomized study in high-risk patients with neutropenia compared the two approaches: an empirical strategy, defined as treatment of persistent or recurrent fever, and pre-emptive management, defined as treatment of patients with clinical, imaging or galactomannan-testing evidence of fungal disease.[33] Patients were treated with either amphotericin B deoxycholate or liposomal amphotericin B, depending on renal function. The pre-emptive approach was non-inferior to empirical treatment for survival; 95.1% of patients were alive at 14 days in the pre-emptive group compared with 97.3% in the empirical group. However, the incidence of probable or proven infections during induction therapy was higher in the pre-emptive group (12/73 pre-emptive versus 3/78 empirical, $P<0.01$).[33] Similar results were achieved in another study in which allogenic HSCT recipients were randomized to either empirical therapy or PCR-based pre-emptive treatment, with liposomal amphotericin B in both groups. There were no differences in survival at 100 days but more patients in the pre-emptive group received liposomal amphotericin B compared with the empirical group (57% versus 37%; $P<0.0001$).[34] Nevertheless, the empirical antifungal approach is still widely used in high-risk patients with neutropenia when prompt diagnostic work-up cannot be performed. Based on the results of a randomized double-blind trial in which liposomal amphotericin B (as empirical therapy) showed similar efficacy compared with amphotericin B deoxycholate, but fewer breakthrough fungal infections, less infusion-related toxicity and less nephrotoxicity, liposomal amphotericin B became the standard.[35]

Liposomal amphotericin B was subsequently compared with both voriconazole and caspofungin in open-label non-inferiority trials. In the first trial, voriconazole did not meet the protocol-defined criteria of non-inferiority to liposomal amphotericin B

with regard to overall response, and consequently voriconazole did not receive regulatory approval for empirical treatment of febrile neutropenia.[36] However, caspofungin showed a similar overall success rate to liposomal amphotericin B and thus fulfilled the statistical criteria of non-inferiority. The proportion of patients who survived at least 7 days after therapy was greater in the caspofungin group (92.6% versus 89.2%; $P=0.05$).[37] Based on the results of this trial, caspofungin was also approved for the empirical treatment of IFIs.

Impact of new haematology treatments

In recent years, the treatment landscape for haematological malignancies has evolved considerably, which has had a substantial impact on the risk of IFI in patients with AML and allogeneic HSCT recipients. Numerous very effective drugs have been introduced for the treatment of both acute and chronic haematological malignancies, but many have characteristics that are changing our knowledge with regard to the prophylaxis and treatment of IFIs.

A major problem arises because many of these drugs are metabolized by CYP3A4, and most third-generation azoles (e.g. voriconazole, posaconazole) are inhibitors of this cytochrome system, resulting in the potential for important drug–drug interactions that can cause serious haematological and extra-haematological toxicities if administered simultaneously.[38] This presents haematologists with a serious dilemma of how best to balance optimal antineoplastic treatment with the need for antifungal prophylaxis. Usually, anti-leukaemic chemotherapy is prioritized, but this results in the possibility of an increased risk of an IFI, as reported in a recent study with venetoclax.[39]

Changes in the epidemiology of IFIs also affect patients with CLL and indolent lymphomas, who must now be considered a new risk group for fungal complications. There has been a marked improvement in the outcomes of these patients with the introduction of Bruton's tyrosine kinase inhibitors (e.g. ibrutinib, acalabrutinib, zanubrutinib).[40] Historically, this group of patients has not been given antifungal prophylaxis due to the low risk of IFIs; however, various studies have shown an increased rate of IFI, mainly IA, in patients treated with ibrutinib, the most studied drug in this class.[41,42] Ibrutinib, in addition to a suppressive effect on lymphocytes, which are the main target, also acts by suppressing the activity of macrophages, thereby increasing the susceptibility to IFIs.[43] As with the new drugs for AML, there is also a problem of drug–drug interactions between Bruton's tyrosine kinase inhibitors and azoles. Considering the large number of patients and the long duration of treatment, there is no place for routine antifungal prophylaxis unless subsets of patients at greater risk can be identified. Continuous and careful microbiological follow-up seems more appropriate than antifungal prophylaxis, with prompt initiation of antifungal treatment if an IFI is suspected.

The relevance of the introduction of new targeted haematology treatments for the epidemiology and management of IFIs is discussed in more detail in the third manuscript in this supplement.

Role of liposomal amphotericin B in the ICU

Over the past two decades, advances in our understanding of the pathophysiology of fungal infections and progress in the diagnostic armamentarium have led to a spectacular increase in the prevalence of IFIs in critically ill patients.[44,45] The increased proportion of immunocompromised patients in the ICU led to the development of specific management strategies for the diagnosis and treatment of IFIs in patients with haematological malignancies, solid tumours, solid organ transplants or therapy with immunosuppressive drugs (Table 2).[46] However, even in non-immunocompromised patients, yeast and mould infections have been increasingly reported.[45,47] Candidaemia and/or deep-seated candidiasis, as well as all invasive forms of pulmonary aspergillosis, are the main reported fungal infections.[48,49] IFIs caused by Mucorales spp., *Fusarium* spp. and *Scedosporium* spp. are also observed in the ICU but remain rare.[50]

Non-immunocompromised patients with uncontrolled diabetes mellitus and those with open wounds contaminated with Mucorales are at risk of developing invasive forms of the fungal disease with typical features of necrotizing lesions of the lungs or skin and soft tissues, as well as debilitating rhinosinusoidal involvement.[45] In general, patients with mucormycosis receive a substantial part of their care in ICUs. Tissue invasion by non-septate hyphae confirms the diagnosis of mucormycosis; however, early diagnosis based on positive PCR results has not only led to increased recognition of this dreadful disease but might also have resulted in improved outcomes.[51] Control of underlying predisposing conditions, rapid surgical resection and administration of liposomal amphotericin B are the main therapeutic actions.

Candidaemia and invasive candidiasis are often acquired in the hospital or the ICU;[52] however, diagnosis remains limited by suboptimal sensitivity and specificity of blood cultures and diagnostic tools. Despite innovative therapeutic strategies borrowed from the haematology field, which remain mostly unproven[45,53] yet have led to unprecedented use of antifungal agents,[54–56] almost half of critically ill patients with invasive candidaemia die.[49]

As echinocandins have been recommended as first-line treatment in invasive candidiasis, and azoles are widely prescribed, recent changes in *Candida* epidemiology should be considered with caution. In Europe, *Candida albicans* represents 57% of cases, followed by *Candida glabrata* and *Candida parapsilosis*.[57] In India, *Candida tropicalis* is the most common pathogen identified in candidaemia,[58] whereas *C. albicans* and *C. parapsilosis* predominate in Latin America.[59] Importantly, echinocandin-resistant *C. glabrata* has been found in about 10% of cases in the USA, with azole cross-resistance in up to one-third of isolates.[60] In addition, recent outbreaks of MDR *Candida auris* in critically ill patients have been reported.[61]

There are three specific features of candidaemia and/or invasive candidiasis that deserve specific attention in the critically ill. First, intra-abdominal candidiasis must be considered; this can result from perforation, anastomotic leaks, repeat laparotomies, necrotizing pancreatitis or abdominal organ transplants.[62,63] In a consensus of multinational experts, Bassetti *et al.*[62] suggested that empirical antifungal treatment with echinocandins or lipid formulations of amphotericin B should be strongly considered in critically ill patients or those with previous exposure to azoles and suspected intra-abdominal infection who are at high risk of *Candida* infection; subsequent de-escalation is also recommended. Second, for catheter-related candidaemia, in which

Table 2. The place of lipid formulations of amphotericin B in the treatment of patients with *Candida*, *Aspergillus* and Mucorales infections

Title	Ref	Place of lipid formulations of AMB	Additional comment
A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts	62	Empirical antifungal treatment with echinocandins or lipid formulations of AMB should be strongly considered in patients with previous exposure to azoles.	
ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients	65	If catheters cannot be removed, lipid-based AMB or echinocandins should be preferred over azoles. Native valve endocarditis and ocular candidiasis require liposomal AMB ± flucytosine when the susceptibility of the isolate is unknown.	
Diagnosis and therapy of *Candida* infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy	100	Liposomal AMB as a secondary alternative.	
Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America	101	Lipid formulation of AMB is a reasonable alternative to echinocandins in patients without neutropenia in cases of intolerance or resistance. Lipid formulation of AMB is an effective but less attractive alternative in patients with neutropenia.	Strong recommendation; high-quality evidence. Strong recommendation; moderate-quality evidence.
Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline	21	Liposomal AMB is recommended for species with intrinsic high azole MICs (2 mg/mL) or when the mould-active azoles voriconazole and/or isavuconazole cannot be given/are not tolerated.	Strength of recommendation: A
Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America	11	Lipid formulations of AMB should be considered in settings in which azoles are contraindicated or not tolerated.	Strong recommendation; moderate-quality evidence.
Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium	10	First-line treatment with high-dose liposomal AMB is strongly recommended. Isavuconazole and posaconazole are recommended with moderate strength.	Consensus recommendations.

AMB, amphotericin B.

the predominant mode of device-related infection is probably biofilm formation, consideration should be given to the activity of antifungal agents against *Candida* spp. growing in biofilms. Indeed, in animal models, amphotericin B lipid complex and anidulafungin reduced the numbers of *Candida* cells in biofilms, while fluconazole did not.[64] It is strongly recommended to change catheters (not over a guidewire) to shorten the duration of candidaemia and improve survival rates.[65,66] When catheter removal is not possible, a lipid-based amphotericin B formulation or an echinocandin is preferable. Third, septic shock is a clinical feature reported in about 40% of patients with invasive candidiasis or candidaemia.[67] This clinical vignette is of utmost importance as it has emphasized the importance of timing of antifungal therapy and control of the source (i.e. mostly catheter removal). In a retrospective cohort study of 274 patients with septic shock and blood cultures positive for *Candida*, Kollef *et al.*[68] reported a 52.8% case fatality rate in patients with both adequate source control and antifungal therapy administered within 24 h of the onset of septic shock. However, patients who did not achieve these goals had a mortality rate of 97.6%. In addition, Bassetti *et al.*[69] reported an overall 30 day mortality rate of 54% in 216 patients with septic shock and candidaemia; inadequate source control and antifungal therapy were predictors of mortality. Septic shock was also a risk factor for mortality in unselected patients with candidaemia and those with cirrhosis and candidaemia.[70,71]

Aspergillus is found in the lower respiratory tract of up to 2% of non-immunocompromised critically ill patients without neutropenia who are receiving mechanical ventilation.[72,73] In line with this, autopsy studies report a 1% prevalence of invasive pulmonary aspergillosis that was not suspected at the time of death.[74] However, more recent post-mortem data report higher prevalence of IA, especially in patients receiving steroids and those with COPD.[75] *Aspergillus* is also found in the lower respiratory tract of 8.3% of patients with acute respiratory distress syndrome (ARDS), and half of these cases were eventually considered as colonization.[76] However, an earlier autopsy study in patients with ARDS reported that 15% of the patients had evidence of invasive pulmonary aspergillosis,[45] a finding consistent with the number of patients with ARDS receiving veno-venous extracorporeal membrane oxygenation who presented with positive *Aspergillus* samples.[77] Interestingly, in patients with suspected ventilator-

associated pneumonia, the prevalence of *Aspergillus* infection was found to be 12.4% (95% CI 8.1–17.8).[78] In a retrospective study in seven centres, the Dutch–Belgian Mycosis Study Group reported that 19% of patients with influenza pneumonia developed invasive pulmonary aspergillosis compared with 5% of patients with 'classic' community-acquired pneumonia.[79] Lastly, in patients with severe COVID-19 pneumonia, the prevalence of invasive pulmonary aspergillosis has been reported to be 3%–30%.[80] Current guidelines recommend voriconazole as first-line treatment for IA based on a randomized controlled trial published in 2002, in which voriconazole showed significantly higher survival rates and fewer severe adverse events compared with conventional amphotericin B.[18,21] Liposomal amphotericin B is a second-line option in refractory cases, when voriconazole is contraindicated or if the *Aspergillus* isolate has a voriconazole MIC ≥2 mg/L.

Paediatric use

Liposomal amphotericin B is one of the few antifungal agents approved for use in children aged 1 month to 18 years. Two other formulations of amphotericin B are approved for use in infants and children: conventional amphotericin B deoxycholate and amphotericin B lipid complex. This is in contrast with the mould-active azoles; voriconazole is approved for use in children aged ≥2 years, while itraconazole, posaconazole and isavuconazole are not approved by the EMA for use in children. The FDA has approved itraconazole and posaconazole for use in children aged ≥13 years. Of the echinocandins, only caspofungin and micafungin are approved for use in children. Liposomal amphotericin B has a broad spectrum of activity, few drug–drug interactions and no requirement for therapeutic drug monitoring. Antifungal therapy is often started in children on clinical suspicion of IFI because of the challenges in diagnosis and high case fatality rate. Due to this combination of factors, liposomal amphotericin B is one of the most frequently prescribed and administered mould-active antifungal agents in paediatric patients.[81,82]

The pharmacokinetic data available show that liposomal amphotericin B can be prescribed in children using the same dosing recommendations as for adults, and no dose-limiting toxicity has been found with dosages up to 10 mg/kg/day.[83–85] Liposomal amphotericin B has a favourable safety profile in children, but there is an increased occurrence of hypokalaemia and infusion-related vomiting with doses above 5 mg/kg/day.[83,84,86,87]

Recommendations for use of liposomal amphotericin B can be found in a number of international guidelines, including three paediatric-specific management guidelines,[88–90] although these recommendations are mainly based on data derived from trials in adult patients. Nevertheless, three clinical trials have assessed the efficacy of liposomal amphotericin B as an empirical antifungal agent in children,[91–93] and one Phase III efficacy trial included 105 paediatric patients (total 687 patients).[35] Two studies compared the efficacy of caspofungin versus liposomal amphotericin B in 138 high-risk children with febrile neutropenia (caspofungin, $n=87$; liposomal amphotericin B, $n=51$) and found no difference between the two groups.[91,92] Prentice *et al.*[93] compared the safety and efficacy of conventional amphotericin B deoxycholate 1 mg/kg/day ($n=63$), liposomal amphotericin B 1 mg/kg/day ($n=70$) and liposomal amphotericin B 3 mg/kg/day ($n=71$) in the treatment of febrile neutropenia in 204 children. No significant difference was observed in efficacy between the three groups (51% versus 64% versus 63%, respectively), but significantly fewer adverse events and drug-related allergies were reported in the liposomal amphotericin B groups ($P<0.01$). The results from these trials underpin the strong recommendation for both caspofungin and liposomal amphotericin B as empirical antifungal therapy in paediatric patients.[90] Two single-centre paediatric antifungal prescription studies showed that liposomal amphotericin B is the preferred choice for empirical and pre-emptive therapy in paediatric patients in 32% and 48% of cases.[81,82] A prospective observational study including 55 children showed an overall response rate (a composite of all five of the following criteria: successful treatment of any baseline fungal infection; absence of any breakthrough fungal infection during therapy or within 7 days after the completion of therapy; survival for 7 days after the completion of therapy; no premature discontinuation of study therapy because of drug-related toxicity or lack of efficacy; and resolution of fever during neutropenia) of liposomal amphotericin B for febrile neutropenia of 54.5% in paediatric patients, which was higher than for adult and elderly patients (47.5% and 42.1%, respectively).[94] Discontinuation due to toxicity or lack of efficacy was significantly less frequent ($P<0.01$) in paediatric patients (18.2%) compared with adult and elderly patients (38.7% and 47.9%, respectively).

For targeted treatment in children with cancer or undergoing HSCT, liposomal amphotericin B is recommended as first-line treatment for invasive candidiasis and mucormycosis, and as second-line treatment for IA.[90] Comparable recommendations are found in IFI-specific paediatric guidelines.[88,89] Only one efficacy trial for invasive candidiasis, which compared liposomal amphotericin B (3 mg/kg/day) versus micafungin (2 mg/kg/day), has included children; 84 patients aged between 1 month and 16 years were randomized in this trial.[95] Sub-analyses showed comparable treatment success rates of 76.0% and 72.9%, respectively. The use of higher dosages of liposomal amphotericin B (5–10 mg/kg/day) is recommended in guidelines for invasive mucormycosis and invasive mycoses affecting the CNS.[10,90]

Published multicentre experiences have demonstrated that liposomal amphotericin B is the preferred antifungal choice for probable and proven invasive fungal disease in paediatric patients.[96,97] A higher proportion of children were treated with liposomal amphotericin B for a diagnosis of invasive mucormycosis compared with other invasive mycoses.[96] All 15 paediatric patients with invasive mucormycosis in a multicentre study in Italy were treated with liposomal amphotericin B, often combined with surgery, with 80% receiving a higher dosage between 5 and 10 mg/kg/day.[98]

In summary, liposomal amphotericin B is well tolerated in paediatric patients aged 1 month to 18 years and there is comprehensive clinical experience with this antifungal agent in children. Its relatively frequent use in paediatric patients is related to its broad spectrum of activity and the limited number of alternatives, as only a few antifungal agents are licensed for use in children.

Conclusions

Medicine is a constantly expanding and dynamic field. New interventional surgical and non-surgical techniques and targeted immunosuppressive therapies for adults and children are being

rapidly introduced, including in the haemato-oncology setting and in ICUs. Therefore, novel groups of patients at risk of invasive fungal diseases are constantly being identified. Most recently, complicated infections with influenza A/B and severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) have been identified as independent risk factors for fungal superinfections. While *Candida* and *Aspergillus* spp. remain the dominant offending fungal pathogens, rarer species (such as those of the Mucorales order) are clearly on the rise.

The echinocandins have been identified as drugs of choice for the first-line treatment of invasive *Candida* infections based on their excellent safety and efficacy profiles. However, resistance is becoming a major issue, especially with *C. glabrata* and during recent outbreaks of *C. auris*. Historically, mould-active azoles have been recommended for the first-line treatment of IA, given their proven efficacy and ease of administration. However, more recently, their pole position has been challenged by the presence of azole resistance, unexpected and difficult-to-manage acute and particularly long-term toxicities, unpredictable pharmacokinetics with the need for therapeutic drug monitoring, and high potential for inhibition of essential CYP450 enzymes (e.g. 3A4), resulting in hazardous interactions when combined with some of the novel small molecules with a narrow therapeutic window. In addition, azoles have been suggested for treatment of invasive mucormycosis, but only for those patients who are unable to tolerate the higher doses of liposomal amphotericin B or with underlying renal impairment that precludes the use of amphotericin B-based therapy.

Liposomal amphotericin B has a drug profile that meets many of the shortcomings of the alternative drugs: a broad spectrum of activity with a low risk of resistance; predictable pharmacokinetics with a rapid accumulation at the infection site (including biofilms); a low risk of drug–drug interactions; and a low risk of acute and chronic treatment-limiting toxicities. Disadvantages of liposomal amphotericin B are the lack of an oral formulation and a low risk of moderate-to-severe renal impairment. Hence, liposomal amphotericin B is an excellent candidate for the first-line treatment of patients with suspected fungal infection, based on prolonged neutropenic fever not responding to antibacterial therapy (the 'empirical' approach) or based on a mycological marker or radiological feature of IFI (the 'pre-emptive' approach). In addition, liposomal amphotericin B is an excellent alternative for patients with documented fungal disease who can no longer tolerate or continue their first-line azole or echinocandin therapy, both in the haematology setting and in the ICU. Moreover, it is one of the recommended pillars in the treatment of invasive mucormycosis, in addition to surgical debridement and better control of the underlying conditions. Finally, liposomal amphotericin B is one of the few antifungals approved for use in children of all ages above 1 month.

Therefore, liposomal amphotericin B, after more than 30 years of use, still has a fixed and even indispensable place in our therapeutic arsenal in the fight against lethal fungal infections in all patient groups.

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Author contributions

All authors contributed to the design of the review, undertook literature research, wrote sections of the review, reviewed the other sections and approved the final version.

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