Invasive fungal diseases in children with hematological malignancies and stem cell transplant recipients

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Abstract

Invasive Fungal Disease (IFD) remains a major cause of morbidity and mortality in patients with hematological malignancies or undergoing stem cell transplantation. New surrogate markers of IFD -galactomannan antigen, β-D-glucan, fungal polymerase chain reaction...and the availability of modern antifungal drugs have changed the management of this serious complication, but both have limitations in children. There are still some unclear issues, particularly in pediatric patients, regardless of the medical and economic possibilities of hospitals: IFD remains difficult to diagnose in a timely way, stem cell transplant recipients have different risk of IFD, antifungal drugs are not free from adverse effects and prospective studies in children are scarce. In this sense, diagnosis criteria have to be assessed, risk stratification should be redefined and the different types of prophylaxis/treatment -prophylaxis, preemptive, empiric and targeted treatment- must be used correctly. We consider low risk for IFD children undergoing autologous stem cell transplantation and children with acute lymphoblastic leukemia; both should receive fluconazole as primary prophylaxis and empiric therapy with an agent with activity against mold. In those who undergoing allogeneic stem cell transplantation or chemotherapy for acute myeloid leukemia, prophylaxis should be performed with a mold active agent -triazoles priority-. We rarely use preemptive therapy because of a high false positive rate of galactomannan. In proven and probable IFD we use targeted therapy, selecting a drug based on the type of infection, sensitivity to the drug in our hospital and prior antifungal prophylaxis/treatment. In selected patients, antifungal combination therapy should be a valid option. Despite great advances, there are still thought provoking questions on the diagnosis and management of IFD in children with hematological diseases.

Key words

Invasive fungal disease, Children, Hematological diseases, Stem cell transplantation

1 Introduction

Invasive Fungal Disease (IFD) remains a crucial problem in patients with hematological pathologies or undergoing stem cell transplantation [1-3]. Despite the improvement in critical care and the advent of new antifungal drugs [4, 5], the use of more aggressive therapies and prolonged neutropenia heightens the chances of developing fungal infections [6, 7]. The incidence of IFDs has significantly increased in pediatric cancer patients and has been recently found to be 21% in acute lymphoblastic leukemia, 15% in acute myeloid leukemia and 25% following stem cell transplantation [8]. The majority of these IFDs are caused by Aspergillus spp. and Candida spp. [9-13] but recently others IFDs like Zygomycetes, Fusarium...
spp. or *Scedosporium* spp. appear in an increasing percentage [14], probably due to the use of a mold active agent as antifungal prophylaxis [15, 16]. The most frequent isolated *Aspergillus* is *A. fumigatus* [13, 17]. Moreover, there are several differences between children and adults in the diagnostic markers and, of course, on the availability, pharmacokinetic, safety and efficacy of antifungal drugs [18]. In this review, we discuss the way and difficulties we have in the diagnosis of IFD in children with hematological pathologies and options for the best practices in treating them.

2 Diagnostic criteria

An early diagnosis of IFD is one of our main goals when we meet a high-risk pediatric patient, because early and appropriate treatment is critical for survival [19]. This diagnosis begins with an assessment of risk that includes several issues like primary hematological disease, depression of the cellular immune status, particularly the intensity and duration of neutropenia, and immunosuppressive therapy [20]. Children undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), induction and consolidation chemotherapy for acute myeloid leukemia and reinduction chemotherapy for relapsed acute lymphoblastic leukemia are high-risk patients for developing IFD [21]. Children with these conditions should be monitored closely with daily physical examinations and scheduled laboratory microbiological tests. We should reserve diagnostic imaging tests for patients with suspected IFD in order to avoid unnecessary exposure to radiation [22]. One of the main problems we face in the IFD diagnosis in children is the lack of evidence of laboratory tests like Galactomannan Antigen (GM), 1-3 \( \beta \)-D glucan and *Aspergillus* and Fungal Polymerase Chain Reaction (PCR), which have been proven to be successful in adults and less so in children [23]. It is often difficult to collect appropriate tissue specimens for culture or histology; fungal cultures lack sensitivity [24, 25] and histological diagnosis requires invasive procedures. In the diagnosis of IFD, we use the revised European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [25].

2.1 Galactomannan antigen test

GM is a measurable biological marker in the extracellular fluid during the growth of *Aspergillus* hyphae and cell wall turnover. US Food and Drug Administration approved the standardized methods for GM detection based on antigen enzyme immunoassay. After promising results in adults [26], it has shown controversial and disappointing results with low sensitivity in children; high false positive rates due to piperacillin/tazobactam or amoxicillin/clavulanate antibiotic treatment [27, 28], cow’s milk components [29] and *Bifidobacterium* spp. [30]. Moreover, Marr et al. indicated that antifungal therapy decreases sensitivity of GM in adults [31], leading to false negative results, which is also likely to occur also in children.

Steinbach et al. performed a prospective study in pediatric allo-HSCT recipients. Patients undergoing cord blood allo-HSCT received prophylaxis with voriconazole and the remaining with fluconazole with a GM >0.5 considered positive. GM test showed a per-patient specificity of 87.3%, but it was higher (91.5%) when excluding samples from patients receiving piperacillin/tazobactam [32]. Hayden et al. reported a study in 56 hematology-oncology pediatric patients of whom 17 had proven or probable invasive aspergillosis (IA), sensitivity and specificity were 65.7% and 87% respectively, using a GM cut-off of 0.5. They obtained a positive GM result in most cases before clinical or radiographic evidence of infection [33]. Castagnola et al. published their experience in 195 periods at risk in children with cancer or undergoing hematopoietic stem cell transplantation; sensitivity was 32% while specificity was 98%, with best results in children following chemotherapy compared with those undergoing allo-HSCT. None of the patients received antifungal prophylaxis against *Aspergillus* and the test result was defined as positive when the GM cut-off was >0.7 in a sample or between 0.5 and 0.7 in at least two consecutive samples [34]. Based on our experience between 2006 and 2010, in children under 14 years undergoing allo-HSCT using voriconazole as primary antifungal prophylaxis, per-episode specificity was 72.2% (unpublished data). The test for galactomannan antigen in the serum was performed twice weekly using AGA EIA (Platelia Aspergillus; BioRad Laboratories) [35]. Galactomannan test results were interpreted as positive when an optical
density index of $\geq 0.5$ was reached in two consecutive measurements or $\geq 0.8$ in one sample\cite{36} and, nowadays, we do not usually use piperacillin/tazobactam.

2.2 1-3 $\beta$-d-Glucan

1, 3-$\beta$-d-Glucan ($\beta$-glucan) is a cell wall component found in several fungal pathogens, including Candida spp. and Aspergillus spp., and can be detected through two commercial kits: Fungitec G-test and Fungitell. Smith et al. found higher $\beta$-glucan levels in non-hematological children, but with several false-positive results\cite{37}. In a recent study in 63 children with acute leukemia, Mokaddas et al. warn of rising levels of $\beta$-glucan in children colonized by Candida without current infection\cite{38}. Although discouraging information is available, new prospective studies are needed in pediatric patients with hematological diseases to validate this test. Until recently, this technique was not routinely used in our hospital.

2.3 Fungal DNA PCR

In the last years, detection of Aspergillus nucleic acid by PCR in bronchoalveolar lavage fluid and serum is another useful tool for the diagnosis of IA. Hummel et al. studied Aspergillus PCR in 71 onco-hematological pediatric patients with suspected IFD, sensibility and specificity were 80% and 81% respectively\cite{39}, while Armenian et al. performed a weekly Aspergillus PCR in children with acute leukemia (n=58) or undergoing allo-HSCT (n=20) finding only 2 positive Aspergillus PCR in 23 patients with IFD (3 probable and 20 possible). He found a high rate of false positives\cite{40}. El-Mahallawy et al. designed a study in high-risk pediatric cancer patients; they used GM and pan-fungal PCR to investigate the diagnostic utility of these markers. Pan-fungal PCR showed sensitivity of 75% and specificity of 92%, while negative PCR in the proven and probable cases was closely related to previous antifungal therapy\cite{41}. Landlinger et al. established a two-reaction real-time PCR assay with highly sensitivity detection of more than 80 fungal pathogens in 125 high-risk children; they presented a sensitivity and specificity of the assay of 96% and 77% respectively, but with a positive predictive value of 62%\cite{42}. Although PCR for Aspergillus may be a useful marker in pediatric patients, especially those on diets rich in dairy products or receiving piperacillin/tazobactam, in our experience the use of Aspergillus PCR has not achieved satisfactory results due to its low specificity. However, it is a technique that should be validated in further prospective studies.

Figure 1. Chest radiography and CT scan of a girl with invasive aspergillosis
2.4 Imaging test

Although chest radiograph usually do not report diagnostic findings, in some patients this test may show interesting images, as in Figure 1. In this way sinus, chest or abdominal Computed Tomography scan is the election test in the early detection of IFD. However, these imaging studies also lack specificity related to fungal species. In a multicenter retrospective analysis of 139 pediatric patients with IA, Burgos et al. showed that the most frequent radiological finding was nodules in 59% of children followed by cavitation, halo sign and air-crescent sign in 24.5%, 10.9% and 2.2% of children, respectively [13]. Abdominal ultrasound is the imaging modality of choice for children with suspected hepatosplenic candidiasis [43] (Figure 2), although nuclear magnetic resonance can prove lesions not detected by ultrasound [44].

![Figure 2. Hepatosplenic candidiasis lesions detected by abdominal ultrasound in a girl undergoing allogeneic stem cell transplantation.](image)

3 Most commonly used antifungal drugs in children

Despite important achievements and new information available, the use of antifungal agents in pediatric patients is still partially limited by the fact that not all of them are now approved in this population, the appropriate dosage of these drugs has not been definitely established for all age groups due to variable pharmacokinetic and pharmacodynamic properties and data providing information on safety and efficacy of different agents is still insufficient. In Table 1 and in the following lines, we will briefly review the main antifungal drugs used in pediatric patients.

3.1 Azoles

Fluconazole is approved mainly for treating invasive candidiasis and as prophylaxis of IFD in immunocompromised children due to chemotherapy and/or radiotherapy. Voriconazole is approved for treatment of IA, fusariosis and scedosporiosis, and for primary treatment of invasive candidiasis in non-neutropenic patients. There is no data available in children under 2 years old. With regard to posaconazole, the safety and efficacy in children under 18 years of age has not yet been established, but different studies have reported promising results in pediatric patients [45, 46]. Itraconazole is not approved for use in children unless the potential benefits outweigh the risks; anyway some groups have used it with acceptable results [47]. However, severe neurotoxicity has been associated with concomitant use of vincristine [48].

Evidence on the best approach to azole therapeutic drug monitoring is still limited. One of the challenges is to define the optimal threshold levels, especially for voriconazole and posaconazole. It has been suggested a minimum concentration target for voriconazole of >1.7 mg/L, particularly in children and when treating pathogens with higher minimum inhibitory
concentrations (MIC) for voriconazole (e.g., Scedosporium spp.) \cite{49}. However, the therapeutic value of serum level monitoring of posaconazole remains uncertain and based on available evidence, posaconazole cannot be recommended for routine clinical use at this time.

**Table 1. Main antifungal drugs used in hematological adult and pediatric patients**

<table>
<thead>
<tr>
<th>Antifungal Drug</th>
<th>Formulation</th>
<th>Pediatric dose</th>
<th>Adult dose</th>
<th>Indications in hematological children</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmB-D</td>
<td>i.v.</td>
<td>0.3-1.5 mg/kg/24h</td>
<td>0.3-1.5 mg/kg/24h</td>
<td>Severe systemic fungal infections.</td>
</tr>
<tr>
<td>AmB-LC</td>
<td>i.v.</td>
<td>5 mg/kg/24h</td>
<td>5 mg/kg/24h</td>
<td>Severe systemic fungal infections.</td>
</tr>
<tr>
<td>L-AmB</td>
<td>i.v.</td>
<td>3 mg/kg/24h</td>
<td>3 mg/kg/24h</td>
<td>Severe systemic fungal infections. Empirical treatment.</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>i.v.</td>
<td>50 mg/m²/24h</td>
<td>50 mg/m²/24h</td>
<td>Invasive candidiasis. Empirical treatment.</td>
</tr>
<tr>
<td>Micafungin</td>
<td>i.v.</td>
<td>2-4 mg/kg/24h</td>
<td>150 mg/24h</td>
<td>Invasive candidiasis. Antifungal prophylaxis. *Use if others antifungals are not appropriate.</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>i.v.</td>
<td>1.5 mg/kg/24h</td>
<td>100 mg/24h</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>i.v., oral</td>
<td>6-12 mg/kg/24h</td>
<td>200-400 mg/24h</td>
<td>Invasive and superficial candidiasis. Antifungal prophylaxis.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>i.v., oral</td>
<td>7 mg/kg/12h</td>
<td>4 mg/kg/12h</td>
<td>Invasive aspergillosis, candidiasis, scedosporiosis and fusariosis.</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>oral</td>
<td>Not available</td>
<td>400 mg/12h</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>i.v., oral</td>
<td>3-10 mg/kg/24h</td>
<td>100-200 mg/24h</td>
<td></td>
</tr>
</tbody>
</table>


### 3.2 Echinocandins

In children, caspofungin is currently approved as a treatment for invasive candidiasis, treatment of IA refractory to other antifungal agents as well as for empirical therapy in neutropenic patients. In children under 16 years, micafungin is approved for the treatment of invasive candidiasis and prophylaxis of *Candida* infection in patients undergoing allo-HSCT or with neutropenia expected for more than 10 days, while anidulafungin has not been approved in children although Cohen-Wolkowiez et al. performed a study showing that children who received 1.5 mg/kg/day reached levels similar to adults receiving 100 mg/kg/day \cite{50}.

### 3.3 Amphotericin B

Renal impairment is a strong limitation for amphotericin B deoxycholate \cite{51} and should not be routinely used in children. Amphotericin B lipid complex and, especially, liposomal amphotericin B (L-AmB) have less renal toxicity. Infusion...
related side effects are substantially less frequent only with L-AmB. Now, L-AmB is approved for empirical therapy in persistently neutropenic patients and for invasive mycoses treatment, being the treatment drug of choice for invasive mucormycosis [32].

4 Treatment

Four different approaches are available for the clinical management of IFD: prophylaxis and three types of therapy -empiric, preemptive and targeted-. We should use the most appropriate in every patient. In all approaches, we have to evaluate the benefit, cost and potential side effects of the chosen drug. There is another important issue: the knowledge of the most prevalent IFD in our institution and its sensibility to different antifungal drugs. In the list below children are divided according to the risk for fungal infection and in Figures 3 and Figure 4 we present an algorithm to approach management of these hematological pediatric patients.

HIGH-RISK

- Allogeneic hematopoietic stem cell transplantation.
- Acute myeloid leukemia: induction or consolidation chemotherapy.
- Acute lymphoblastic leukemia: reinduction chemotherapy.
- Aplastic anemia (expected <200/mm³ neutrophil count >14 days).

LOW-RISK

- Autologous hematopoietic stem cell transplantation.
- Acute lymphoblastic leukemia: induction chemotherapy.

![Figure 3. Proposed algorithm for the management of children with hematological diseases and low-risk of fungal infection](image-url)
Figure 4. Proposed algorithm for the management of children with hematological diseases and high-risk of fungal infection.

1. Clinical criteria: persistent fever despite treatment with broad-spectrum antibiotics.
2. Computed tomography scan, ultrasound, nuclear magnetic resonance.
3. GM-: GM negative or not available.
4. Micafungin is the only echinocandin with indication for prophylaxis.
5. Consider using voriconazole if the patient is receiving a prophylaxis with an echinocandin.
6. If imaging studies are compatible with IFD caused by filamentous fungi you should not use an echinocandin in monotherapy.

* Voriconazole is not approved for children under 2 years and caspofungin is not approved for children under 1 year.

4.1 Prophylaxis

Prophylaxis should be used in patients at risk of IFD. Many centers have conducted additional prophylaxis trials aiming to reduce the incidence and mortality of IFD [53-55] after allo-HSCT, but children are frequently excluded due to lack of an appropriately characterized or unknown dosage. For years, fluconazole has been the gold standard drug for prophylaxis in hematological patients undergoing aggressive chemotherapy or stem cell transplantation [56]. Dvorak et al. performed a study using Amphotericin B deoxicholate or fluconazole as antifungal prophylaxis with an IFD rate of 13% [57]. Mehta et al. reported 15 pediatric patients who received antifungal prophylaxis with micafungin (3 mg/kg/48 hours), the drugs reached good serum levels and no patient developed IFD [58]. Kolve et al. used L-AmB as primary or secondary prophylaxis in children (3.5% IFD in the global series) [59] and van Burik et al. used micafungin only during neutropenic phase (2.5% of IFD) [60]. Mandhaniya et al. prospectively compared oral voriconazole (4 mg/kg/12 hours) versus intravenous low dose of conventional amphotericin B (0.5 mg/kg/day thrice weekly) as primary antifungal prophylaxis in pediatric acute leukemia (both lymphoblastic and myeloid) induction. Voriconazole was comparable with amphotericin B with less toxicity and more convenience [61].

We recently published a series of 56 children undergoing allo-HSCT using primary prophylaxis with voriconazole (5 mg/kg/12 hours or 7 mg/kg/12 hours), only one of them with acute graft versus host disease developed IFD (probable aspergillosis) on day +130, but 10 (17.8%) patients presented adverse effects related to voriconazole, easily resolved once the drug was stopped [62]. Compared to our previous strategy, using fluconazole prophylaxis, the incidence of IFD, from January 2000 to October 2004, in pediatric patients who underwent allo-HSCT was significantly higher than with voriconazole prophylaxis (12.1% vs.1.8%, p = .03). A total of 33 children received an Allo-HSCT in this time; four of them developed IFD: three pulmonary aspergillosis and one invasive candidiasis, with a mortality of 75%. Similarly, we published our results using Voriconazol as primary antifungal prophylaxis in patients with neutropenia after HSCT or chemotherapy for acute myeloid leukemia [54], including 16% of pediatric patients, showing an overall treatment success.
rate of 72.9%, with a reduced use of empirical therapy (17%), and in contrast to data described by Trifilio et al. [15], we did not find an increase of breakthrough zygomycosis.

Wingard et al. compared fluconazole with voriconazole in patients (including children) who had undergone allo-HSCT and differences did not reach statistical significance in terms of IFD incidence, but they did not study children separately from adults [63]. Ullman et al. conducted a randomized study that showed that posaconazole was superior in preventing IA and reducing the rate of deaths related to fungal infections in patients with graft versus host disease [55], while Cornely et al. indicated that in patients undergoing chemotherapy for acute myeloid leukemia or myelodisplastic syndrome, posaconazole prevented fungal infections more effectively than did either fluconazole or itraconazole but with more serious adverse events [64]. However, in both studies children under 13 years were not included.

4.2 Empirical treatment

Empirical treatment is used in high-risk children with persistent or recurrent fever despite broad-spectrum antibiotic therapy, without radiological or microbiological evidence of IFD. There is only a randomized, double blind, multicenter trial published comparing caspofungin with L-AmB for empirical antifungal therapy in 82 pediatric patients (60 with hematological diseases) with persistent fever and neutropenia without differences in safety and efficacy [65]. Recently, Caselli et al. conducted a randomized study that evaluated empirical antifungal therapy in 110 neutropenic children with persistent fever and found high-risk patients as the target for empirical antifungal therapy in contrast to the low-risk [66]. Koo et al. evaluated the efficacy and safety of caspofungin for the empirical treatment in neutropenic children, 79% of courses resulted in a favourable response while 25% of courses experienced an adverse-drug-related event attributed to caspofungin [67].

4.3 Preemptive treatment

There are no studies addressing preemptive therapy for IFD in children with hematological diseases, so this approach should be not recommended in pediatric patients. The most important work about this issue was published by Maertens et al. who called for early initiation of antifungal therapy, while reducing empirical therapy, using GM and Computed Tomography for early diagnosis, but all patients were older than 16 years [68]. Subsequently, Cordonnier et al. compared empiric versus preemptive antifungal treatment in a multicenter, open-label, randomized trial in patients over 18 years and it was found that preemptive treatment increased the incidence of IFD without increasing mortality [69]. Pagano et al. had similar results when comparing preemptive vs. empiric antifungal therapy, but in this study children were not included [70]. Finally, Tan et al. in a study in 52 episodes in high-risk hematological patients concluded that a preemptive approach may reduce empirical antifungal use without differences in twelve-week survival rates in persistently febrile neutropenic patients, but this work did not include children [71]. We rarely use preemptive therapy because of the high false positive rate of GM and Aspergillus PCR.

4.4 Targeted therapy

Once an IFD has been diagnosed, we must initiate targeted therapy. The choice of specific drug relies on several variables: the antifungal drug used for prophylaxis or empirical treatment, the patient’s clinical conditions, type of fungal infection and sensitivity of fungi to different antifungals in each institution. We have considered that one of the main points is the restoration of the host immune response, particularly in our experience granulocyte recovery [72] joined to an early and appropriate treatment [73].

International guidelines recommend using an echinocandin or lipids formulations of amphotericin B, particularly L-AmB because of its lower rate of side effects, in children with invasive candidiasis while voriconazole can be used when additional coverage for molds is desired [74]. Recently, several non-albicans Candida species are occurring with increasing frequency [75]: especially Candida glabrata that should preferably be treated with an echinocandin, and Candida krusei, which can be treated with an echinocandin, L-AmB or voriconazole.
In contrast to adult patients, prospective randomized studies have not been performed in children with hematological malignancies and diagnosed with IA. Nevertheless, children have been placed together with adults in published studies, but unfortunately in most of them, children has not been analyzed separately from adults and, in addition, not all patients in the studies were diagnosed with hematologic diseases. Voriconazole is currently the first-line treatment of choice for IA based on the data reported by Herbrecht et al. that established the significant superiority of voriconazole vs. amphotericin B in patients with IA \cite{76}. L-Amb is also a valid treatment option for IA and caspofungin may be used in children who are refractory or intolerant to other antifungal agents \cite{77}.

<table>
<thead>
<tr>
<th>Fungal Infection</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharyngeal Candidiasis</td>
<td>Fluconazole 6-12 mg/kg/24h</td>
<td>L-AmB 3 mg/kg/24h</td>
</tr>
<tr>
<td>Oropharyngeal Candidiasis</td>
<td>Fluconazole 6-12 mg/kg/24h</td>
<td>voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Candidemia</td>
<td>Fluconazole 6-12 mg/kg/24h</td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Candidemia</td>
<td>Fluconazole 6-12 mg/kg/24h</td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Hepatoesplenic Candidiasis</td>
<td>L-AmB 3 mg/kg/24h</td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Hepatoesplenic Candidiasis</td>
<td>L-AmB 3 mg/kg/24h</td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Invasive Aspergillosis (pulmonary,</td>
<td>L-AmB 3 mg/kg/24h</td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Mucormycosis (pulmonary, rhinosinusual, cerebral...)</td>
<td></td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Mucormycosis (pulmonary, rhinosinusual, cerebral...)</td>
<td></td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Fusariosis</td>
<td>Voriconazole 7 mg/kg/12h</td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
<tr>
<td>Scedosporiosis</td>
<td>Voriconazole 7 mg/kg/12h</td>
<td>Voriconazole 7 mg/kg/12h</td>
</tr>
</tbody>
</table>

L-AmB: liposomal amphotericin B, mg: milligram. kg: kilograms. m: meter. h: hour.

L-AMB is the drug of choice for invasive mucormycosis whereas posaconazole can be used as rescue therapy or when L-AmB should be discontinued because of unacceptable adverse effects. This therapy must be supplemented with an early surgical debridement of affected tissues \cite{52} and local therapy as amphotericin B ointment or instillation \cite{78}. Since 2004 we have only diagnosed a rhino-orbital mucormycosis in a 13 year old boy with aplastic anemia successfully resolved by surgical treatment, L-AmB and posaconazole. Voriconazole and L-AmB are the drugs of choice for the treatment of invasive infection caused by \textit{Fusarium} spp. \cite{79} and \textit{Scedosporium} spp. \cite{80}, whereas posaconazole can be used as salvage therapy for these infections. In Table 2 are summarized the targeted therapy of most important fungal infections.
4.5 Combined antifungal therapy

There are no randomized trials comparing monotherapy versus combination antifungal therapy in pediatric population. Although international guidelines do not recommend it [81], the availability of new agents with different modes of action has led to use them in combination for selected patients, particularly the combination of an echinocandin with a mold-active azole or L-AmB with promising results [82-84]. We recently published a retrospective study in hematological patients diagnosed with IFD and treated with antifungal combination therapy. This study included children and 62% of patients achieved a favourable response whatever the combination antifungal used [72]. By contrast, Kontoyiannis et al. conducted a study in patients with IA treated with micafungin alone or in combination with other antifungals reporting a response rate of 26% and 19% in the global series and in the pediatric population, respectively [85]. Mihu et al. reported a retrospective study in 159 hematological pediatric and adult patients and they found that the combination of L-AmB and echinocandins did not offer advantage over either drug alone [86]. A randomized clinical trial in adult patients with hematological diseases or undergoing stem cell transplantation is now completed and will provide more insights on the general usefulness of antifungal combinations in first line therapy [87]. A study in children using voriconazole plus anidulafungin for IA has been withdrawn [88].

4.6 Adjuvant therapy

Despite the availability of new antifungal compounds, morbidity and mortality of IFD, particularly in pediatric Allo-HSCT recipients remains unacceptably high. The past decade has witnessed an exciting improvement of the understanding of the molecular pathogenesis and the complexity of host antifungal immune responses. Strategies for enhancing the immune system include the administration of effector cells (e.g., granulocytes, antigen-specific T cells, dendritic cells) as well as the administration of recombinant cytokines, interferons and growth factors (e.g., interferon-γ, keratinocyte growth factor, granulocyte and granulocyte-macrophage colony stimulating factor). In this sense, granulocytes transfusion has been used in neutropenic patients with aspergillosis, despite the lack of evidence of safety, efficacy and appropriate doses [89].

In pediatric patients with hematologic malignancies and diagnosed with IFD another adjuvant therapies can improve survival outcome; in children with hepatoesplenic candidiasis the use of corticosteroids added to antifungal drug as a treatment for immune reconstitution inflammatory syndrome, is associated with prompt resolution of the symptoms once neutrophil recovery occurs [90, 91].

Iron chelation with deferasirox was a promising adjuvant therapy in adults [92] but Spellberg et al. observed that patients with mucormycosis treated with deferasirox and L-AmB had a higher mortality rate at 90 days and concluded that these data do not support a role for initial adjunctive deferasirox therapy for mucormycosis [93]. Hyperbaric oxygen is another adjuvant therapy for mucormycosis but clinical data are very limited [94].

5 Future directions

5.1 Nonstandard diagnostic techniques

In addition to detection of fungal cell wall components (β-glucan and galactomannan) and fungal-related nucleic acids, newer nonculture-based assays are being investigated to improve the early diagnosis of IFD caused by Candida,
Aspergillus and other fungal pathogens. These methods include antibodies or antigens (e.g., mannan) and metabolites (e.g., L/D-arabinitol) [95]. It has begun to explore whether diagnosis can be improved by a combination of both methods [96].

5.2 Host susceptibility to invasive fungal disease
There is a large body of evidence that there is a genetic component leading to the susceptibility and outcome of IFD in immunocompromised patients. In allo-HSCT recipients, several genes polymorphisms in both host and donor, has been described to significantly predispose patients to IFD (TLR1 & TLR6; IL-10 promoter; Plasminogen; TLR4; Chemokine Ligand 10; Dectin-1) [97]. Future research will likely discover additional polymorphisms that lead immunocompromised hosts at an increased risk of IFD.

5.3 Investigational antifungal agents
In parallel with the rise in the frequency and spectrum of IFD, several new antifungal agents have been developed. These agents optimally should reduce toxicity, improve bioavailability and overcome resistance to conventional drugs. Most data of investigational antifungal agents such as albaconazole, isavuconazole, ravuconazole, aminocandin, MK-3118 and E1210 are limited to animal studies or Phase I/II studies in humans [98-100]. As common features, these antifungal agents share extended half-lives, good tolerance and low drug interaction profiles. In addition to activity against Candida and Aspergillus spp., they have a broad spectrum activity against resistant and emerging pathogens. However, adequate randomized clinical trials will provide more information to assess the real potential of these agents in the future.

6 Conclusions
Invasive Fungal Disease is a life-threatening infection in patients with hematological malignancies or undergoing stem cell transplantation. An accurate definition of risk, an aggressive diagnostic approach and an effective and proper use of different types of treatment should lead to a progressive success in solving these serious complications in adults and children, without forgetting that children are not small adults, so we need to know the main differences in the diagnosis and treatment of IFD in both.

Competing interests
JR. Molina has received honoraria for speaking at medical education events supported by Gilead Science and Pfizer. R. Rojas has received honoraria for speaking at medical education events supported by Gilead Science and Merck Sharp & Dohme (MSD). J. Serrano and P. Gómez declare no competing financial interest.

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