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Review

Clinical practice update of antifungal prophylaxis in immunocompromised children

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ABSTRACT

Due to the rise in the number and types of immunosuppressed patients, invasive fungal infections (IFI) are an increasing and major cause of morbidity and mortality in immunocompromised adults and children. There is a broad group of pediatric patients at risk for IFI in whom primary and/or secondary antifungal prophylaxis (AFP) should be considered despite scant evidence. Pediatric groups at risk for IFI includes extremely premature infants in some settings, while in high-risk children with cancer receiving chemotherapy or undergoing haematopoietic stem cell transplantation (HCT), AFP against yeast and moulds is usually recommended. For solid organ transplanted, children, prophylaxis depends on the type of transplant and associated risk factors. In children with primary or acquired immunodeficiency such as HIV or long-term immunosuppressive treatment, AFP depends on the type of immunodeficiency and the degree of immunosuppression. Chronic granulomatous disease is associated with a particular high-risk of IFI and anti-mould prophylaxis is always indicated. In contrast, AFP is not generally recommended in children with long stay in intensive care units. The choice of AFP is limited by the approval of antifungal agents in different age groups and by their pharmacokinetics characteristics. This document aims to review current available information on AFP in children and to provide a comprehensive proposal for each type of patient.

Key-words: antifungal prophylaxis, children, pediatric patients, HIV, primary immunodeficiency, Solid organ transplantation, haematopoietic stem cell transplantation.

Revisión de estrategias de profilaxis antifúngica en niños inmunodeprimidos

RESUMEN

Las infecciones fúngicas invasoras (IFI) constituyen un problema creciente en adultos y niños inmunodeprimidos, acompañándose de una elevada morbimortalidad. El número de niños inmunodeprimidos va en aumento. Los grupos de riesgo de IFI en pediatría incluyen a los grandes prematuros, que se benefician de profilaxis con fluconazol, pacientes hemato-oncológicos sometidos a quimioterapia o trasplante de precursores hematopoyéticos con neutropenias prolongadas, en quienes la profilaxis frente a hongos filamentosos suele recomendarse en situaciones de alto riesgo. En niños sometidos a trasplante de órgano sólido, la profilaxis depende del tipo de trasplante y factores de riesgo asociados. En pacientes con inmunodeficiencias primarias o adquiridas como la infección VIH o tratamiento inmunosupresor prolongado, la profilaxis antifúngica dependerá del tipo de inmunodeficiencia primaria y del grado de inmunosupresión. La enfermedad granulomatosa crónica tiene riesgo particularmente elevado de IFI y requiere siempre profilaxis frente a hongos filamentosos. En cambio, en niños con ingresos prolongados en cuidados intensivos la profilaxis frente a IFI habitualmente no está indicada. El tipo de profilaxis está limitado por la diferente aprobación de antifún-

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gicos a distintas edades. Este documento pretende revisar la información actual disponible respecto a profilaxis antifúngica en niños, con propuesta para la estrategia más apropiada en cada tipo de paciente.

Palabras clave: profilaxis antifúngica, niños, pacientes pediátrico, VIH, inmunodeficiencia primaria, trasplante de órgano sólido, trasplante de precursores hematopoyéticos

Invasive fungal infection (IFI) is considered an opportunistic infection that occurs almost exclusively in immunocompromised and critically ill children. The impact of an IFI can be devastating and is associated with a high rate of morbimortality despite the availability of new antifungal drugs in recent years.

The number of paediatric patients at risk for IFI is increasing and include: extremely premature infants (especially those with weight less than 1,500 g), children with cancer, undergoing haematopoietic stem cell transplantation (HSCT) or solid organ transplant, neutropenic children, those with long stay in intensive care units (ICU) and children with primary or acquired immunodeficiency such as HIV or long-term immunosuppressive treatment [1-4]. Timely diagnosis and initiation of appropriate antifungal therapy is a key point to improve outcomes. Thus, it is mandatory to consider antifungal prophylaxis (AFP) in most of these situations. Herein, a comprehensive proposals for each patient´s group based on an updated review of AFP strategies in children is provided.

The strength of recommendations and the quality of evidence are graded according to the scoring system proposed by the Infectious Diseases Society of North America (IDSA) [1]. In the process of providing recommendations, we have taken into account the paediatric development regulations and guidelines from the European Medicines Agency (EMA). The EMA accepts the requirement for extrapolation of evidence for efficacy from studies in adults to paediatric patients or from older to younger paediatric patients when the following criteria are met: (a) underlying condition and cause of targeted disease and expected response to therapy are similar; (b) data from clinical studies on pharmacokinetics, safety and tolerance are available for paediatric patients; and (c) supportive paediatric efficacy data exists [2]. In this scoring system, the strength of the recommendation is rated as follows: A: strongly recommended; B: moderately recommended; C: weak author support; D: not recommended by the authors. The quality of evidence is evaluated on a 3-level scale as follows: I: data from at least 1 well-designed and conducted randomized controlled trial; II: data from at least 1 well-designed and conducted clinical trial, without randomization, cohorts or case-control analyses (preferably multicenter), multiple retrospective series, or major findings of noncontrolled studies; III: expert opinions based on clinical experience, descriptive case series, or expert committee reports [1].

1.- ANTIFUNGAL PROPHYLAXIS IN NEWBORNS

The prevalence of invasive candidiasis (IC) is highly variable in neonatal intensive care units (NICU) ranging from 3% to 23% in extreme premature infants, depending on the complexity of the NICU and whether surgery is involved or not. This patient population has a high risk of dissemination to the central nervous system (up to 15-20% in extreme premature babies), even before presenting overt clinical signs of infection, and high mortality rates. Despite high variations among NICU, *Candida albicans* is the most frequent isolated species, followed by *C. parapsilosis* [3-6].

Risk factors for IC in preterm infants include immaturity of the immune system (especially low levels of maternal IgG transmission and impaired functions of opsonization and complement) and epithelial barriers, frequent rupture of these barriers by invasive procedures, such as catheters, intubation or surgery, and the increase in the density of colonization by *Candida* spp. promoted mostly by the frequent use of broad-spectrum antibiotics. In addition, H2-receptor blockers and steroids may facilitate intestinal translocation leading to *Candida* spp. invasion and secondary systemic infection. Transmission through peripartum colonization and horizontal transmission through health-care professionals colonized by *Candida* spp. may also occur [3-6]. Due to its bad prognosis, prophylactic strategies to prevent IF are warranted [7].

General strategies include hand hygiene; individual room for families and newborns; reduction of risk factors for colonization and infection for IC, such as limitation of H2-receptor blockers, steroids and broad-spectrum antibiotics, mainly carbapenems and third-generation cephalosporins; minimizing the use of invasive devices including minimal manipulation of central venous catheters, as well as early introduction of mother´s milk. Although some experts advocate for using lactoferrin alone or combined with probiotics in order to reduce intestinal *Candida* spp. colonization and late onset sepsis in neonates weighing < 1,500 g, evidence is still scarce [7] (CII).

The indication of AFP, although controversial, is generally recommended in preterm babies <1,000 g., in NICU with a prevalence of *Candida* spp. infection above 5-10%. Oral nystatin suspension (1ml: 100.000 U/ml) has been considered as an option, when fluconazole is not available or azole resistance is suspected, but evidence is low [7] (CII). When indicated fluconazole is the recommended option, starting either in the first 24 or 72 hours of life at a dose 3-6 mg/kg i.v. (until catheter withdrawal) or orally twice weekly for 6 weeks. Multiple clinical trials have been performed with several regimens of fluconazole showing the impact of fluconazole in high-risk preterm babies in the incidence of IC, morbidity and mortality [8-12]. Twice weekly regimens do not seem to be inferior to the same daily dose [10]. According to the IDSA guidelines prophylaxis with fluconazole is indicated in admitted neonates with birth weight < 1000 gr when the prevalence of IC is higher than 10% [1]. Similarly, above this threshold in Spain, different Spanish scientific societies (Spanish Society of Infectious Diseases and Clinical Microbiology -SEIMC- and Spanish Society of Paediatric Infectious Diseases-SEIP) advocate fluconazole prophylaxis at 3 mg/kg/day in newborns with birth weight < 1,500 g, continuing it for all the period at risk [4,13]. The ESC-

MID strongly recommends it in NICU with a prevalence higher than 5% of IC in babies <1,000 g at birth at a dose of 3-6 mg/kg twice weekly i.v. or orally [14]. Also, the Latino American working group of invasive fungal infections recommends fluconazole prophylaxis 3 mg/kg twice a week, in newborn weighing < 1,000 g for 6 weeks in NICU with prevalence of IC ≥ 5% [15] (AI). In NICU with a prevalence < 5% fluconazole prophylaxis should be individualized and considered only in preterm neonates with multiple risk factors for IC (<1,000 g, need for a prolonged central vascular central and broad-spectrum antibiotics (CII) [14].

Fluconazole prophylaxis is a safe strategy, and although isolates of *Candida* spp. with reduced susceptibility to azoles have been described, there is no evidence of development of clinical emergence of resistance to azoles in newborns after prolonged exposure. Although there are few studies with long-term follow-up, there is no evidence for any relationship with neurocognitive impairment, blindness, deafness or cerebral palsy at 24 months of life, nor impact on growth. Even though fluconazole may lead to increased liver enzymes, significant liver toxicity is uncommon with prophylaxis dosages [12].

Filamentous fungi are infrequent in the neonatal period, and have only rarely been reported in preterm babies, including *Aspergillus* spp. and *Rhizopus* spp., albeit associated with a very high mortality [16]. Micafungin is approved in newborns including preterm but its activity against moulds is limited. Voriconazole use has been anecdotical, although it is not approved below 2 years of age [16, 17]. Due to its potential retinal toxicity in particular in the immature preterm retina, no clinical trials are planned in this age group [18]. Thus, specific AFP against moulds in this patient group is not recommended [2].

2.- ANTIFUNGAL PROPHYLAXIS IN THE PAEDIATRIC INTENSIVE CARE SETTING

Indications for primary prophylaxis in non-immunocompromised critically ill children are not clear. Despite a relatively high incidence of IFI in patients admitted at the Pediatric Intensive Care Unit (PICU), evidence for primary and/or secondary AFP in non-immunocompromised critically ill children is lacking.

In the intensive care setting, by far the predominant IFI are due to *Candida* spp., being filamentous fungi anecdotical, and therefore, AFP if considered, should be targeted only against yeasts. Some authors, based on different prediction scores, recommend AFP in adults for invasive candidiasis, with fluconazole (CII), or as an alternative an echinocandin like caspofungin in non-immunocompromised high-risk patients, although the grade of recommendation is low (CIII) [19, 20]. Risk factors for invasive candidiasis identified in this population include: abdominal surgery with recurrent perforations, intubated patients for more than 48 h and expected to be ventilated for another 72 hours, multiple *Candida* spp. colonization, systemic antibiotics, central venous catheters, transfusion and *Candida* spp. positive urine cultures [20, 21]. However, these criteria might not be fully applicable to children.

Several studies have tried to identify risk factors for invasive candidemia in non-immunocompromised critically ill children. In one population-based, case-control study in a large tertiary care paediatric center, the following risk factors for *Candida* spp. bloodstream infections were identified: presence of central venous catheter, underlying malignant conditions, and having received vancomycin or an anti-anaerobic antibiotic for more than 3 days. The predicted risk for candidemia for patients with some of these three risk factors in different combinations ranged between 10% and 46%. In this study, the authors concluded that these patients could be candidates for antifungal prophylaxis [4].

Another observational study in 24 Spanish PICUs recorded 125 invasive *Candida* spp. infections and determined that previous bacterial infection, chronic metabolic disease, digestive surgery, pre-PICU stay longer than 15 days, previous colonization, parenteral nutrition and invasive devices were risk factors [22]. Central venous catheters, immunosuppression (including long-term steroids), damage of gastrointestinal tract, broad-spectrum antibiotics, parenteral nutrition, renal failure requiring hemodialysis, mechanical ventilation and genetic susceptibility have been described in other studies as important risk factors [23-25]. Children younger than one year of age have a higher incidence of candidemia [26].

In addition to risk factors, the local incidence of invasive *Candida* spp. infections should be considered to decide whether or not to start AFP. An incidence of 10% is considered the threshold to use prophylaxis with an acceptable risk-benefit analysis. Some authors suggest that in PICUs with rates of invasive candidiasis higher than 5%, AFP may be considered in selected patients with several risk factors (CII).

There are few studies about the benefits of AFP in PICU. Reduction on invasive candidemia incidence with fluconazole prophylaxis has been studied in adult intensive care patients in four meta-analyses, though the incidence of both candidemia and mortality decreased only in two of these studies. Even though evidence is scarce especially in children, prophylaxis may be an option in selected critically ill children, other than immunocompromised and oncological patients, considering the high mortality of these infections. A personalized assessment may be warranted for individual PICU patients based on the presence of specific individual risk factors and local epidemiology

The difficulty to identify risk factors for invasive *Candida* spp. infections and the lack of evidence about the benefits of AFP, make early empirical treatment a preferred strategy for children with a high likelihood of fungal infection in order to decrease the high mortality rates [14] and minimizing the selection of antifungal resistances. Empiric therapy for non-neutropenic patients with risk factors for fungal infections without documented invasive candidiasis is still controversial [27]. Decision should be based on colonization data, presence of risk factors, surrogate markers of fungal infection and ongo-

ing fever despite proper antibiotic treatment. In the absence of microbiological confirmation nor clinical response, therapy should be maintained no more than 4 or 5 days [1].

In adults, daily bathing of the patients admitted in the intensive care units in chlorhexidine has been studied in one trial for its role as a protective factor for *Candida* spp. bloodstream infections [28]. Even though significant impact on *Candida* spp. infection is not proven, the measure is easy, inexpensive and may be beneficial. The impact in paediatric intensive care units is still to be determined.

In conclusion, current recommendations about prophylaxis should be individualized considering the PICU epidemiology, as well as the individual predisposition and colonization (CII).

The balance between overuse of antifungal agents with emerging resistance and efficacy is yet to be determined and better evidence in the paediatric intensive care setting has to be collected.

3.- CANCER PATIENTS AND STEM CELL TRANSPLANT RECIPIENTS

3.1 Risk factors for invasive fungal disease

Children receiving treatment for cancer or undergoing haematopoietic stem cell transplant (HSCT) have a significant risk of developing IFI, with high morbidity and mortality**.** Risk factors for IFI in these patients are conditioned by the breakdown in natural barriers, defects in cell-mediated immunity and mainly deficient the presence of profound and persistent neutropenia (table 1) [29, 30].

Primary AFP is generally recommended for those children whose risk is greater than 10% (table 2) [29, 31, 32]. However, in the choice of an appropriate AFP strategy it is important to consider some modifiers like the local epidemiology, comorbidities or specific treatment modalities. New therapies such as tyrosine kinase inhibitors and other immunomodulatory therapies (i.e. CAR T-cell therapy [33] broad the spectrum of patients at risk for IFI [34], so the assessment of risk should be individualized.

3.2 Primary antifungal prophylaxis

Whereas pharmacokinetic/pharmacodynamic (PK/PD) and safety of the different antifungal agents are targeted in paediatric studies; the evidence for efficacy may need to be extrapolated from studies in adult population. Although there are only few antifungal agents currently approved for AFP in children, an increasing number of reports describe safety and suggest efficacy of agents given to prevent IFI in the pediatric population. In addition, most studies do not address the optimal dosage of an antifungal agent to prevent IFI. The final choice of an antifungal drug for prophylaxis should be individualized based on the patient risk, the agent activity, the toxicity profile, and the PK/PD data [29, 32].

The specific recommendations for AFP are summarized in table 3 based on the different risk groups. There are not specific prophylaxis recommendations for the new drug classes for haematological and oncologic conditions (i.e. tyrosine kinase inhibitors], and it remains unclear if AFP is indicated in these cases [34]. Table 4 presents the different antifungal agents used for AFP. Azoles are the preferred drugs for prevention of IFI, considering anti-mould active agents in high-risk patients. Caution is advised for concomitant use of triazoles with chemotherapy metabolized by cytochrome P450 isoenzymes. Options include itraconazole (AII); posaconazole for patients ≥13 years of age (AII) and voriconazole for patients >2 years of age (AII). Echinocandins and liposomal amphotericin B represent alternatives when azole-

Table 1 Risk factors for IFI

Clinical factors	Severe and persistent neutropenia[a]
	Lymphopenia
	Mucosal damage
	Central venous catheters
	Previous fungal colonization
	Graft versus host disease (GVHD) in HSCT
	CMV infection in HSCT
Pharmacological factors	Steroids in high-doses[b]
	Anti-tumour necrosis factors agents
	Alemtuzumab
	Nucleoside analogues
	CAR T-cell therapy

IFI: invasive fungal infection, HSCT: haematopoietic stem cell transplant, CMV: cytomegalovirus, CAR: chimeric antigen receptor

[a]Absolute neutrophil count of ≤500 cells/µL for >7-10 days

[b]Steroids in pharmacological doses (≥0.3 mg/kg per day prednisone or equivalent)

Table 2 Stratification of risk for IFI

High-risk (≥ 10%)	Acute myeloid leukemia
	Recurrent or high-risk acute lymphoblastic leukemia
	Allogeneic HSCT[a]
	Severe aplastic anemia
Low-risk (≤ 5%)	Standard-risk acute lymphoblastic leukemia
	Autologous HSCT[b]
	Non-Hodgkin's lymphoma
Sporadic	Pediatric solid tumors
	Brain tumors
	Hodgkin's lymphoma

HSCT: Haematopoietic Stem Cell Transplant. GVHD: Graft versus Host Disease. IFI: invasive fungal infection.

[a]Pre-engraftment phase or with associated GVHD.

[b]In the neutropenic phase it could be considered intermediate-risk.

Table 3 **Antifungal primary prophylaxis in children with cancer: recommendations based on risk groups [31, 32, 34–39]**

Underlying condition	Cancer	Comments
Children undergoing allogeneic HSCT with no GVHD		
AFP is recommended during the neutropenic phase until engraftment (BII)	Fluconazole (AI)	Only active against yeasts
AFP is recommended after engraftment until discontinuation of immune suppression and immune recovery (no grading)	Itraconazole (BI)	TDM recommended
	Voriconazole (BI)	TDM recommended
	Micafungin (CI)	
	Liposomal amphotericin B (CIII)	
	Posaconazole (no grading)	For children ≥13 years
		TDM recommended
Children undergoing allogeneic HSCT in the presence of GVHD (acute grade II–IV or chronic extensive) treated with augmented immunosuppression		
AFP against mould and yeast infections is recommended while the immunosuppression is maintained (AII)	Posaconazole (BI)	For children ≥13 years
		TDM recommended
	Voriconazole (BI)	TDM recommended
	Itraconazole (CIII)	TDM recommended
	Liposomal amphotericin B (no grading)	
	Micafungin (no grading)	
Autologous HSCT with anticipated neutropenia >7 days		
AFP should be considered (BI) until immune recovery	Fluconazole (AI)	
	Micafungin (AII)	
	Any mould active agent (DIII)	
Paediatric de novo or recurrent leukemia patients		
AFP should be considered in high risk patients (BII).	Itraconazole (BI)	TDM recommended
No evidence-based recommendations can be made on the	Posaconazole (BI)	For children ≥13 years
duration in patients with persisting neutropenia in this group		TDM recommended
	Liposomal amphotericin B (BII)	
	Fluconazole (CI)	Active only against yeast
	Other options include: Voriconazole (no grading)	
	Micafungin (no grading)	

AFP: Antifungal prophylaxis. TDM: Therapeutic Drug Monitoring. HSCT: Haematopoietic Stem Cell Transplant. GVHD: Graft versus Host Disease

based regimes are contraindicated or not tolerated. Options include liposomal amphotericin B (BII); micafungin (BII); and, with less strength of evidence, aerosolized liposomal amphotericin B (CII) and caspofungin (CII) [31, 34, 35]. In the absence of GvHD, AFP may be continued after engraftment until discontinuation of immunosuppression and signs of immune recovery. In the presence of GvHD requiring augmented immunosuppression (including steroids in therapeutic dosages or anti-inflammatory antibodies), prophylaxis against IA and other relevant IFI is recommended (AII) [2]. Newer agents, such as isavuconazole, are under study in children, and have poor evidence to be recommended for AFP.

3.3 Secondary antifungal prophylaxis

Despite the scant data in children, secondary AFP or continued antifungal treatment after an episode of invasive mould infection is recommended based on the high rate of relapse (30–50%) [31]. The drug of choice should be active against the previous fungal pathogen. Secondary AFP should continue for as long as the patient is neutropenic or immunosuppressed (AII), e.g. allogeneic HSCT (early phase), chemotherapy resulting in severe neutropenia (i.e. <500/mL and at least for 7 days), acute GVHD > stage II, extensive chronic GVHD, or T-cell suppressing therapy, including steroids. Currently evidence is

Table 4 **Agents and antifungal dosing recommended in haemato-oncological or HSCT paediatric patients [31, 32, 37, 40].**

Antifungal agent and dosing	Dosing	Spectrum	Comments
Fluconazole	6–12 mg/kg/day QD IV/PO (maximum 400mg/day)	Only against yeast	
Itraconazole	5 mg/kg/day BD PO (>2 years of age)	Both yeasts and moulds	Not approved in patients <18 years. TDM required
Voriconazole	2 to <12 years or 12–14 years and <50 kg: 16 mg/kg/day BD IV/PO (first day: 18 mg/kg/day IV/PO BD) >15 years or 12–14 years and >50 kg: 8 mg/kg/day BD IV/PO (first day: 12 mg/kg/day BD IV; 400 mg/day BD PO)	Both yeasts and moulds (no against *Zygomycetes*)	Not approved in patients <2 years. TDM required. Increased risk of phototoxicity.
Posaconazole	600 mg/day TDS PO (suspension) in patients >13 years [41] 300 mg/day QD PO (3 x 100 mg delayed-release tablets). First day: 600 mg/day BD. 300 mg/day QD IV (first day: 300 mg/day BD)	Both yeasts and moulds	Limited PK data in patients <13 years. Not approved in the European Union in patients <18 years. TDM required. Coverage for most fungi, including *Zygomycetes*. Delayed released tablet formulation presents better PD data. Taken with food.
Liposomal amphotericin B	1 mg/kg IV every other day or 2.5 mg/kg IV twice weekly	Both yeasts and moulds	Still not approved for prophylaxis in children [32, 42]. Optimal dose of alternate administration is still unknown. Alternative when azole based regime is contraindicated or not tolerated.
Caspofungin	50 mg/m^2/day QD IV (first day: 70 mg/m^2/day QD IV) (maximum 70 mg/day)	Both yeasts and moulds	Caspofungin does not have a label for the prophylactic Indication [43].
Micafungin	1 mg/kg/day (if >50kg : 50mg) QD IV	Both yeasts and moulds	Approved for AFP of *Candida* spp. infections in granulocytopenic children. Less interactions than azoles with other drugs. Considerably higher drug clearance in children 4 months to 5 years compared to older children.

QD: once daily. BD: twice a day. TDS = three times a day. AFP: antifungal prophylaxis. For interactions, see table 6.

lacking regarding the minimal duration of the therapy before the continuation of anticancer treatment of the conditioning regime for allogeneic HSCT [31, 40].

3.4 Practical aspects

3.4.1 Therapeutic drug monitoring (TDM)

The objective of monitoring the plasma levels of antifungals is to optimize their dose, in order to improve efficacy and minimize toxicity. This is important in children, because of their pharmacokinetic variability, and especially in hematology-oncology patients who have multiple conditions (associated with their underlying disease and its treatment) that affects the absorption, distribution, metabolism and clearance of antifungal medications [44]. TDM is generally recommended during prophylaxis with itraconazole, voriconazole and posaconazole (AII). Recommended plasma target ranges are summarized in table 5 [40, 45]. Usually, the first sample should be acquired

Table 5 Recommended plasma target ranges for antifungal drugs

Antifungal	Prophylaxis plasma range	Treatment plasma range	Quality of evidence
Itraconazole	0.5-4 mg/L	1-4 mg/L	AII efficacy
			BII toxicity
Voriconazole	1-6 mg/L (optimal 2-5 mg/L)		AII efficacy
			AII toxicity
Posaconazole	>0.7 mg/L	>1 mg/L	BII efficacy (prophylaxis)
			AII efficacy (treatment)

within 5-7 days of starting therapy (2-5 days for voriconazole) and repeated until steady-state level in the therapeutic range is confirmed, if there are changes in the patient's clinical condition, concomitant medications, or suspected toxicity [40].

3.4.2 Side effects and drug-drug interactions

The main side effects of the antifungals used in prophylaxis and relevant interactions for hematology-oncology patients are summarized in table 6.

3.4.3 Monitoring of fungal biomarkers

Serum galactomannan (GM) screening should not be performed in neonates and children at low risk for IA (DIII). Serum GM should not be used as a screening test in asymptomatic patients undergoing AFP; several studies have shown that it has a low positive predictive value in these cases (BII) [46-48]. Therefore, given the low pre-test risk of IA in the context of effective anti-mould prophylaxis, the result of the test would be either negative or false positive in asymptomatic patients, leading to unnecessary diagnostic tests and treatments. The test remains useful to assist the diagnosis of patients with a clinical suspicion of IFI during prophylaxis [40, 46, 47, 49, 50].

4.- SOLID ORGAN TRANSPLANTATION (SOT)

Patients who received a SOT have a higher risk of IFI, being an important cause of morbidity and mortality. *Candida* spp. are the most frequent IFI, followed by filamentous fungi, especially *Aspergillus* spp. [51]. Not all recipients are at the same risk of IFI. The multicenter epidemiological study TRANSNET, conducted in adult population, shows the highest incidence of IFI in small bowel transplant recipients (11.6%), followed by lung (8.6%), liver (4.7%), heart (4%) and pancreas (3.4%) [51]. Data in children are still scarce, but a recent study, conducted in pediatric population revealed an IFI global incidence of 2%, cardiopulmonary and lung transplant showing the highest incidence (12.5% and 11.4% respectively) [52].

AFP in SOT pediatric recipients can decrease colonization, and therefore, the subsequent development of IFI. Nevertheless, universal AFP is not recommended, and its use will depend on the type of transplanted organ and the receptor risk factors to develop an IFI. There are no recommendations in the pediatric field due to the limited published information, so that most of them are adapted from those published in the adult population. In general, patients at high risk (expected incidence higher than 10%) should receive prophylaxis against filamentous fungi (AII). The drug of choice will depend on the type of transplant organ and the population studied [53].

4.1. Prophylaxis against yeasts

Liver, pancreas and bowel recipients have the highest risk to develop an invasive candidiasis, thereby potentially benefiting from AFP. Liver transplant recipients need to meet at least two risk factors [54, 55] (table 7). Fluconazole or echinocandins are the most recommended drugs [56], considering amphotericin B when patients have risk factors for filamentous fungi (AIII). The most recommended duration is 4 weeks in the liver transplant and at least 4 weeks in the pancreas and bowel transplant. In kidney recipients, invasive candidiasis is the most frequent IFI, although its incidence is low, so prophylaxis is not recommended (DIII) [54].

4.2 Prophylaxis against *Pneumocystis jirovecii* (PJ)

The incidence of PJ pneumonia in a study made in adult population in United Kingdom was 5.8% in lung or cardiopulmonary transplants, 5.5% in heart, 1.2% in liver and 0.3% in the kidney recipients [57]. Prophylaxis against PJ during the first months after the transplantation is recommended in several guidelines for adults and children [58]. Trimethoprim sulfamethoxazole (TMP-SMX) is the drug of choice [57, 59]. In case of intolerance to cotrimoxazole, dapsone is the second line drug more used for prophylaxis, although less effectivity has been observed in some pediatric studies [60]. There is little experience with atovaquone and pentamidine (inhaled or intravenous).

The duration of PJ prophylaxis is not established, ranging between 3 and 12 months after the transplantation according to different scientific societies [59, 61]. Its indication should be prolonged after graft rejection or higher steroid needs (over 20 mg of prednisolone or ≥0.3 mg/kg or equivalent for more than 4 weeks). It has also been proposed to keep it indefinitely in lung or bowel transplant, in patients with chronic CMV infections and in those with a history of a previous infection by PJ (BII) [57].

4.3 Prophylaxis against filamentous fungi

Invasive aspergillosis (IA) is one of the most relevant fungal infections in SOT recipients, with an overall incidence reported of 1-15%, being higher in lung transplant in surveillance studies (44%) [51], and reported mortality rates of ap-

Table 6 | **Side effects and drug interactions of antifungals used in prophylaxis**

Antifungal	Adverse effects	Interactions
Fluconazole	Gastrointestinal disorders Elevation of transaminase levels	Cyclosporine, ifosfamida, irinotecan, vincristine, fentanyl, omeprazole, ondansetron, cotrimoxazole, prednisone, dexamethasone
Itraconazole	Gastrointestinal disorders Elevation of transaminase levels Periferal neuropathy Negative inotropic effect (less frequent)	Cyclosporine, ifosfamida, irinotecan, methotrexate, etoposide, vincristine, fentanyl, deferasirox, omeprazole, ondansetron, ranitidine, dexamethasone, prednisone
Voriconazole	Gastrointestinal disorders Elevation of transaminase levels Visual disturbances Hallucinations Headache Rash Long QT-syndrome	Ciclosporin, etoposide, ifosfamida, irinotecan, vincristine, fentanyl, cotrimoxazole, ibuprofen, omeprazole, ondansetron, dexamethasone, prednisone
Posaconazol	Gastrointestinal disorders Elevation of transaminase levels Headache Dizziness Periferal neuropathy Electrolyte alterations Long QT syndrome (less frequent)	Cyclosporine, etoposide, ifosfamida, irinotecan, vincristine, fentanyl, omeprazole, ranitidine, dexamethasone, prednisone
Micafungin	Gastrointestinal disorders Headache Phlebitis Elevation of transaminase levels Electrolyte alterations	Sirolimus, nifedipine, itraconazole
Amphotericin B	Hypokalemia Nephrotoxocity Headache Elevation of transaminase levels Infusion reactions	Cyclophosphamide, cisplatin, cytarabine, etoposide, hydroxyurea, ifosfamide, irinotecan, mercaptopurine, methotrexate, temozolamide, vincristine, vinorelbine, dexamethasone, prednisone cyclosporine, aminoglycosides, pentamidine

proximately 22% despite novel treatment modalities. In lung transplant recipients, invasive pulmonary disease has an even higher mortality rate (67–82%) [59]. AFP against *Aspergillus* spp. is recommended in lung transplant recipients (AIII) and in those children exhibiting a high-risk profile (e.g. Model for End Stage Liver Disease score >30, liver failure, renal failure, reintervention) (BIII) [2]. Data of IA in heart recipients are scarce. Reduction of IFI has been observed in those patients with prophylaxis, but no consensus exists. Some authors recommend AFP only in patients with risk factors [2, 54]. Inhaled lipid formulations of amphotericin B are the most studied option, although its optimal dose, formulation and duration has not been defined in adult population. Systemic azoles with anti-mould activity may also be used for IA prevention. The effectiveness and safety of voriconazole prophylaxis has been studied in lung transplant recipients [2]. The IDSA guidelines recommends itraconazole or voriconazole in patients colonized by *Aspergillus* spp., in those with a proven fungal infection in the removed organ, sinusal aspergillosis or in those who have received a unipulmonary transplant [35].

Duration of prophylaxis is unclear, but at least 3- to 4-week treatment or until resolution of risk factors seems appropriate [2]. In lung and high-risk heart transplanted children a more prolonged prophylaxis (3-12 months) is warranted. The drug of choice remains controversial. Lipid amphotericin B has shown

Table 7 | **Risk factors to IFI in children with SOT**

Fungal infection	Solid organ transplant	Risk factors
Candida species	Liver	Retrasplant
		Post-transplant renal failure
		More than one episode of acute rejection during the first month, requiring the use of steroids or monoclonal antibodies
		Colonization by *Candida* spp.
Aspergillus species	Liver	Retrasplant
		Post-transplant renal failure requiring dyalisis
		Pretransplant fulminant liver failure
		Surgical re-intervention
	Intestine-pancreas	Immunosupression
		Acute graft rejection
		Hemodyalisis
		Initial graft rejection
		Anastomosis related issues
		Post-transplant need of laparotomy
		Infection by cytomegalovirus
	Heart	Post-transplant hemodyalisis
		Surgical reintervention
		Colonization or previous infection by *Aspergillus* spp. before or after transplantation
		Infection by cytomegalovirus
		Acute graft rejection

SOT: Solid Organ Transplantation

a significant reduction of invasive fungal infections without a mortality reduction but is limited by its potential for nephrotoxicity. Echinocandins are not nephrotoxic, and promising results have been published in preventive studies focusing on high-risk liver transplant recipients [2].

In paediatric kidney transplant recipients AFP to prevent filamentous fungi is not recommended (DIII) [54]. In small bowel and pancreas recipients transplant, only patients are risk are candidates for prophylaxis against moulds.

Table 8 summarized the indications about AFP in pediatric population after SOT [32].

5.- PRIMARY IMMUNODEFICIENCIES

Patients with primary immunodeficiencies (PID) are often prone to develop recurrent and/or severe infections, autoimmune disorders and malignancies. Infection site, causative pathogens, clinical course and outcome depend on a number of factors such as the underlying gene defect, patients' age, existence of comorbidities and also environmental factors potentially related to pathogen exposure [62]. IFI are a hallmark of underlying immune disorders and PID must always be considered in those patients. There are several PID that may present with both invasive and mucocutaneous fungal infections, caused by moulds and/or yeasts [63, 64].

Neutrophil defects, (severe) combined immunodeficiencies and diseases caused by mutations altering relevant cytokine pathways are among the list of PID that may present with severe fungal infections. Thus, primary or secondary AFP is recommended for most of the diseases below listed (table 9). However, evidence regarding the most appropriate medication, duration, dosing schedule, drug monitoring and dose adjustment is scarce and often extrapolated from adults and/or the onco-haematologic setting (table 4). Chronic granulomatous disease (CGD) is the PID with the highest risk for IFI, particularly IA with incidences ranging from 26% to 45%. Additionally, IA is the most common infectious cause of death. Prevention of IA plays a central role in the clinical management of children with CGD and consists of reducing environmental exposure to moulds and the prophylactic use of antifungals. Itraconazole prophylaxis has shown to significantly reduce IFD in CGD patients and is recommended as prophylaxis (AII). Posaconazole is a

Table 8 | **Recommendations about antifungal prophylaxis in SOT**

Solid organ transplant	Predominant IFI	Antifungal prophylaxis	Doses	Duration
Liver	*Candida* spp.[a]	Fluconazole oral/ iv	6-8 mg/kg/day	4 weeks
		Caspofungin iv	50 mg/m^2/day	
	Aspergillus spp.[a]	In patients with risk factors for *Aspergillus*: Liposomal amphotericin B iv	1 mg/kg/day	
		Caspofungin iv	50 mg/m^2/day	
Lung	*Aspergillus* spp.	Liposomal amphotericin B (until extubation)	1 mg/kg/day	6-12 months
		Inhaled amphotericin B (in extubated patients)	24 mg: - 1st month 3 times / week – later 1 per week	
		Voriconazole oral/iv[b]	Oral <50Kg: 18mg/kg/day divided in two doses >50 Kg:400 mg/day divided in two doses IV <50Kg: 16 mg/kg/day divided in two doses >50 Kg: 8 mg/day divided in two doses	
		Itraconazole oral/iv[b]	5 mg/kg/day divided in two doses	
Heart	*Aspergillus* spp.	Itraconazole oral/ iv	5 mg/kg/día divided in two doses	3-6 months
		Voriconazole oral/iv	See the previous part	
		Caspofungin iv	50 mg/m^2/day	
		Micafungin iv	1 mg/kg/day	
Pancreas	*Candida* spp.	Fluconazole oral/iv	6-8 mg/kg/day	4 weeks
Intestine	*Candida* spp.	Fluconazole oral/iv	6-8 mg/kg/day	4 weeks
		Liposomal amphotericin B	1 mg/kg/day	
		Caspofungin iv	50 mg/m^2/day	
		Micafungin iv	1 mg/kg/day	
Pneumocystis jirovecii Indicated in all types of SOT		TMP-SMX oral/iv	150 mg/m^2/day divided in two doses 3 consecutive days/ week	3-12 weeks
		Dapsone iv	2 mg/kg/day	
		Pentamidine iv	4 mg/kg/ month	
		Inhaled pentamidine	300 mg/ month	
		Atovaquone iv	30 mg/kg/day	

SOT: Solid Organ Transplantation, IFI: invasive fungal infection. iv=intravenous

The proposed doses have been set following prophylaxis in others indications and after a consensus between the authors.

[a]Recommended in patients with risk factors defined in table 1.

[b]Therapeutic drug monitoring is recommended. Targeted prophylaxis plasma level. Voriconazole: ≥1 mg/l, itraconazole: ≥0,7 mg/l.

favourable alternative (CIII). The use of prophylactic recombinant human interferon-γ has shown to decrease the risk of severe infections (including fungal infections) in CGD by 70%, but controversy remains about its use in routine prophylaxis [2, 65-68].

6.- ANTIFUNGAL PROPHYLAXIS IN CHILDREN WITH HIV-INFECTION

6.1 *Pneumocystis jirovecii* (PJ)

Currently, since the advent of potent combined antiretro-

Table 9 **Indication for primary and/or secondary antifungal prophylaxis in primary immunodeficiencies (adapted from Aguilar C et al.) [63]**

Immunodeficiency	Fungi		Antifungal Prophylaxis
	Invasive /systemic	Mucocutaneous	
Chronic granulomatous disease	Frequent (>30%) *Aspergillus* spp. (pulmonary, bone lesions) and other moulds. Yeasts (rare)	CMC (rare)	Primary prophylaxis Itraconazole (AII)[a] Posaconazole (CIII)[b] Voriconazole not recommended (DIII)
Congenital neutropenia	Rare < 10% *Aspergillus* spp. (pulmonary infections) *Candida* spp. (disseminated infections)		The systematic prescription of antifungal prophylaxis is not justified (DIII). For persistent profound neutropenia despite G-CSF, itraconazole prophylaxis can be considered (BIII).
Hyper-IgM syndrome with cellular defect	*Pneumocystis jirovecii* (pulmonary infections)		TMP-SMX
SCID/CID	*P. jirovecii* (pulmonary infections) *Aspergillus* spp. (pulmonary infections) *Candida* spp.	CMC	TMP-SMX (AII) < 1 month of age consider fluconazole > 1 month consider itraconazole
STAT3 deficiency	*Aspergillus* spp.	CMC	If CMC, consider fluconazole If lung damage consider itraconazole (AIII)
CARD9 deficiency [64] (Only fungi from the phylum *Ascomycota*)	Very common (90%) Mostly *Candida* spp. (CNS infection 30%) Also deep dermatophytosis	Rare (10%) CMC or superficial dermatophytosis	Primary prophylaxis: Fluconazole (AIII) Secondary prophylaxis: according to isolated fungus /infections site
STAT1 gain of function	Rare: mostly *Candida* spp.	Very common Mostly CMC	If recurrent and/or severe CMC: Fluconazole (AIII)
APS-1 (APECED)		Restricted to non-invasive candida infections (CMC)	If recurrent and/or severe CMC: Fluconazole (AIII)
IL-12/IFN-gamma axis defect	Rare: *Candida* spp.	CMC	If recurrent and/or severe CMC: Fluconazole (AIII)
IL-17R deficiencies, ACT1 deficiency	*Candida* spp.	CMC	If recurrent and¨/or severe CMC: Fluconazole (AIII)

ACT1: adaptor for IL-17 receptors; APS1(APECED): autoimmune polyendocrinopathy type1; CARD9: caspase recruitment domain-containing protein 9; CID: combined immunodeficiency; CMC: chronic mucocutaneous candidiasis; G-CSF: granulocyte colony stimulating factor; IFN-gamma: interferon gamma; IL17-R: interleukin-17 receptor; SCID: severe combined immunodeficiency; STAT1: signal transducer and activator of transcription 1; STAT3: signal transducer and activator of transcription 3; TMP-SMX: Trimethoprim-sulfamethoxazole

[a]Itraconazole: broadest experience, dosing regimens are different in Europe and the US.

[b]Posaconazole with promising but only short term results.

viral therapy, PJ is most commonly diagnosed in non-HIV infected children [69]. PJ infection occurs in the general population during the first months of life. More than 80% of children aged 2 to 4 years have antibodies against PJ. Approximately a third of infected immunocompetent children will be asymptomatic or have mild respiratory symptoms. PJ pneumonia (PJP) occurs almost exclusively in the immunocompromised child and is an AIDS-defining illness. PJ infection incidence is highest in the first year of life, in particular between 3 to 6 months. The mode of PJ transmission remains to be established, airborne human to human transmission being the likely cause [70].

Chemoprophylaxis is highly effective in preventing PJP and is recommended in all children older than 6 years with CD4 counts < 200 cells/mm^3 or CD4 percentage <15%; in children 1 to 6 years old with CD4 counts < 500 cells/mm^3 or CD4 percentage <15%; and in infants younger than 12 months regardless of CD4 counts or CD4 percentage (AII) [70].

Infants with indeterminate HIV infection status should receive prophylaxis until HIV-infection has been excluded (AIII). PJP chemoprophylaxis is not recommended in infants found to be definitely or presumed HIV-uninfected. The child should not have other laboratory (e.g., no positive virologic test results) or clinical conditions (e.g., no AIDS-defining conditions that can-

Table 10 Recommended drugs for PJP prophylaxis

Antifungal	Doses and route	Frequency	Evidence
TMP-SMX	150 mg TMP /m²/daily vo	12-24h daily or	AI
1st choice		3 consecutive days or	
	Max dose: 320 mg TMP/daily	3 alternating days	
Atovaquone	Age 1-3 and > 24 months: 30 mg/kg/day/vo	Once daily	AI
2nd choice	4–24 months: 45 mg/kg/day/vo		
	≥13 years: 1,500mg/24h		
	Max dose 1,500 mg/daily		
Dapsone	Age >1 month		BI
3rd choice	2 mg/kg/day	Once daily	
	4 mg/kg/week	Once weekly	
	Max dose 100 mg/daily		
	Max dose 200mg/week		
Pentamidine	4 mg/kg/dose/iv	2-4 weeks	BII
	Age > 5 years:		
	300 mg/dosis/nebulized	Once monthly	BI
	Max dose 300 mg iv		

PJP: *Pneumocystis jirovicii* pneumonia, Max: maximum. iv: intravenous
In case of TMP-SMX contraindication (allergy, intolerance, interactions) 2nd choice prophylaxis includes atovaquone (AI) o dapsone (BI). Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone (BI). Intravenous pentamidine can be used in children older than age 2 years when other options are unavailable (BII).

not be explained on the basis of other causes of immunosuppression) or evidence of HIV infection. Presumptive exclusion of HIV infection in non-breastfeeding infants, can be based on two negative virologic test results, one obtained at ≥2 weeks and one obtained at ≥4 weeks of age; a negative test at ≥8 weeks of age or a negative antibody test at ≥6 months of age.

TMP–SMX is the drug of choice for prophylaxis due to its high efficacy, relative safety, low cost, and broad antimicrobial spectrum. It should be administrated during three consecutive or alternating days/week or on a daily base (AI). In case of TMP-SMX contraindication (allergy, intolerance, interactions), second choice prophylaxis includes atovaquone (AI) o dapsone (BI). Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone (BI). Intravenous pentamidine can be used in children older than age 2 years when other options are unavailable (BII).

Discontinuation of PJP chemoprophylaxis should be considered for HIV-infected children after having received cART for ≥6 months and have demonstrated for >3 consecutive months a CD4 percentage ≥15% or CD4 count ≥200 cells/mm^3 for patients aged ≥6 years (BII), or CD4 percentage ≥15% or CD4 count ≥500 cells/mm^3 for patients aged 1 to <6 years (BII) [70].

CD4 percentage and CD4 count should be re-evaluated at least every 3 months and prophylaxis reinstituted if the original criteria for prophylaxis are reached (BIII). PJP prophylaxis should not be discontinued in HIV-infected infants aged <1 year.

As PJ transmission occurs easily, isolation should be strongly considered and sharing a room with another patient with an undiagnosed respiratory illness that could be PJP should be avoided, especially during the first 2 years of life (AIII).

As none of the drugs used to treat and prevent PJP completely eliminates PJ, and prophylaxis is only effective while the selected drug is administered, patients who have experienced an episode of PJP should remain on a prophylactic regimen after treatment until they meet criteria for discontinuing prophylaxis (AIII).

Secondary prophylaxis should be discontinued applying the same criteria as for discontinuing primary prophylaxis. PJP prophylaxis must not to be discontinued in HIV-infected infants aged <1 year. Once PJP prophylaxis has been discontinued, children should be evaluated and followed-up despite normal or high CD4 counts or percentages (AIII). Lifelong prophylaxis should be administered if PJ infection reoccurs in a patient with a CD4 count ≥ 200 cells/mm (CIII). Table 10 summarizes the drugs used for PJP prophylaxis [70].

6.2 Cryptococcosis

As the incidence of cryptococcosis is low in HIV infected children, neither routine testing of asymptomatic children for serum cryptococcal antigen (CIII), nor primary prophylaxis is recommended (BIII). Secondary prophylaxis for a duration of at least 12 months is indicated using fluconazole (AI) or itraconazole (BI) [70].

6.3 Hystoplasmosis

Routine primary prophylaxis for histoplasmosis in children is not recommended (BIII). Prevention of exposure is attempted by avoiding risk factors predisposing to infection such as exposure to contaminated areas, which can result in the inhalation of histoplasma spores.

Prevention of recurrence is attempted using induction therapy (amphotericin B), followed by a consolidation therapy (itraconazole) for a total of at least 12 months. In case of

sustained immunosuppression (CD4 percentage <15% at any age or <150 cells/mm^3 in children aged ≥6 years) as well as in patients suffering from relapse despite appropriate therapy, treatment may be prolonged (AII). Whilst experience with voriconazole is limited in children, fluconazole has been shown to be less effective than itraconazole (CII).

Recommendations regarding discontinuation of secondary prophylaxis are based on data from clinical trials in adults. Once immune reconstitution (CD4 counts >150 cells/mm^3 in children aged>6 years or >15% at any age) is achieved, histoplasma serum antigen is <2 ng/mL (when available) and itraconazole has been given for ≥1 year; treatment may be stopped (CIII). Histoplasma antigen is not available in most Spanish centers. Therapy is to be continued in case of relapse occurring despite appropriate treatment (BIII) [70].

6.4 *Candidiasis*

Candidiasis due to *Candida* spp. is the most frequent fungal infection in HIV infected patients, being mainly localized and limited to the mucosa and the skin (oropharyngeal and oesophageal candidiasis, vulvovaginitis and dermatitis). Invasive candidiasis is less frequent.

Exposure to *Candida* spp. cannot be prevented as they are commensals of the mucosa and the skin. However, the limitation and rational use of antibiotics is fundamental in order to avoid overgrowth of *Candida* spp. Primary and secondary prevention are not indicated [70].

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