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PEDIATRIC FUNGAL INFECTIONS (E ROILIDES, SECTION EDITOR)

Antifungal Prophylaxis in Children Receiving Antineoplastic Chemotherapy

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Abstract

Purpose of the review The purpose of this study was to summarize data on available antifungal prophylaxis of invasive fungal disease (IFD) in children and when it should be administered during antineoplastic chemotherapy.

Recent findings Antifungal prophylaxis should be considered when incidence of IFD is ≥ 10%, as acute myeloblastic leukemia, high-risk acute lymphoblastic leukemia, and second-line therapy for any relapsing leukemia. In absence of specific pediatric studies, data from adults indicate that triazoles, especially posaconazole tablets, could represent the most attractive option, even if some troubles (mainly regarding drug interactions and intestinal absorption) must be underlined. Echinocandins and liposomal amphotericin B (intravenous or nebulized) can represent alternatives in specific conditions. Other infection control measures (hand hygiene, respiratory masks) can represent adjunctive and effective measures.

Summary Antifungal prophylaxis should be implemented in children receiving aggressive chemotherapy for acute leukemia, and triazoles represent the first choice for this purpose.

Keywords Antifungal prophylaxis · Children · Cancer · Acute leukemia · Invasive fungal disease

Introduction

Invasive fungal diseases (IFD) are a major cause of morbidity and mortality in children with cancer [1]. *Candida* spp. and *Aspergillus* spp. are the most frequently identified pathogens [2, 3], but other fungi, e.g., *Fusarium* spp., *Geotrichum* spp., and also *Pneumocystis jirovecii*, can cause severe infections even if with a lower frequency [4, 5].

The epidemiology of IFD is strictly related with the aggressiveness of antineoplastic chemotherapy, being the highest in children receiving first-line treatment for acute myeloblastic leukemia and high-risk acute lymphoblastic leukemia (depending on protocol and risk profile), second-line therapy for any relapsing leukemia, or an allogeneic hemopoietic stem transplant (HSCT) from an alternative donor or in presence of severe acute or chronic graft vs. host disease (GvHD) [1, 6–11]. In spite of the progresses in diagnosis and treatment, mortality is still very high especially in children at highest risk [12]. Therefore, the development of strategies aimed to prevent these infections could be of pivotal importance. Setting up any prophylactic strategy, including against IFD, has to take in account different factors as follows [13]: (i) frequency of the disease in any given patients' population and any single center [1, 6, 9, 14–19], (ii) number of patients that must receive prophylaxis to prevent one single event (number needed to treat—NNT) [20], and (iii) availability of drugs suitable for prophylactic purposes (with adequate spectrum of activity, easy to be administered, effective, associated with few or no adverse event, without any interaction). Availability of pharmacological data (pharmacokinetic/pharmacodynamic, PK/PD), registration for pediatric use, and formulations suitable for administration in children (especially the youngest) are other important conditions not always available [21–23].

In 2014, the 4th European Conference on Infections in Leukemia (ECIL-4) published a comprehensive guideline for the management of IFD in children with cancer [22]. The aim of the present review is to integrate and update these

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recommendations focusing on children receiving antineoplastic chemotherapy or autologous HSCT (also called megatherapy with autologous stem cell rescue).

Population at Risk

Besides the well-known role of prolonged (defined as longer than 10 days) [8, 24, 25] and profound neutropenia (absolute neutrophil lower than 100 cells/μL) [8] in IFD development [26], other risk factors as mucositis, steroid treatment [8], highly intensive antineoplastic protocols [10, 26], and presence of central venous catheter [27] have been classically associated with an increasing incidence of IFD. More recently, other patient-related, genetic factors, like toll-like receptors and dectin-1 polymorphisms [28–31], have been identified as possible further risk factors for the development of invasive mycoses in cancer or allogeneic HSCT patients. The analysis of the epidemiology of IFD observed in different groups of patients suggested a stratification of the risk of IFD in children as high if incidence is ≥ 10%, low if < 5%, or sporadic [22]. For patients undergoing antineoplastic chemotherapy or autologous HSCT, this stratification is confirmed in the everyday clinical practice where the highest incidence of IFD is observed in acute myeloblastic leukemia or any relapsing leukemia [1, 9–11, 14, 18, 32, 33], while IFD are infrequent in solid tumors [19, 34] or after autologous HSCT [16, 19]. Noteworthy, mortality is still high, especially in infections due to molds or in high-risk patients [1, 8, 12]. All these data should be kept in mind when deciding to start a prophylactic strategy, never forgetting than also local epidemiology can play an important role [15].

Primary Antifungal Prophylaxis

Several compounds are available for antifungal prophylaxis, and their effectiveness has been demonstrated in many adults' studies. Unfortunately, adequate clinical trials are lacking in pediatrics as well as approval by Regulatory Agencies of antifungal drugs for this indication in children. Therefore, the use of antifungal prophylaxis in pediatrics is a procedure derived from adults and frequently off-label for indication and/or drug administered [22, 23]. Anyway, at present, pediatric PK/PD data are available for many drugs and therefore, in the case of implementation of an antifungal prophylaxis program administration of antifungal drugs in children, can be considered feasible and safe, especially when therapeutic drug monitoring (TDM) is available to supervise effectiveness and toxicity [22, 35, 36].

In the last few years, several guidelines have tried to establish a correct pharmacological approach to antifungal prophylaxis in pediatric population with hematological or oncological diseases [21, 22, 37], and Table 1 summarizes the presently available drugs and dosages recommended for prophylaxis of IFD in cancer children.

Triazoles represent the principal drug class involved in prophylaxis, but all available options have some issues. Fluconazole is approved for all ages, but it is active only against yeasts (mainly *Candida* spp. and *Cryptococcus* spp), and not against molds. Fluconazole prophylaxis determined a reduction in IFD development in different studies, but no one in children of age less than 12 years [23, 42, 43]. Itraconazole is active against both molds and yeasts, and it is superior to fluconazole in preventing IFD in patients undergoing allogeneic HSCT [44], but it is not approved for patient aged less than 18 years [22]. Moreover, administration of oral solution is necessary to obtain effective plasma concentrations [22], compound that is often discontinued because of side effects [23]. Voriconazole is active against yeasts and molds, and its prophylactic use in children has been described as well tolerated [45], with improved survival in children with acute myeloid leukemia compared with historical controls, even if associated with changing of epidemiology versus more rare fungi [46]. But voriconazole is not approved for use in patients < 2 years of age. Posaconazole is active against molds and yeasts and has been initially demonstrated effective in preventing IFD in adults receiving chemotherapy for myelodisplastic syndrome [47]. Even if not approved in patients < 18 years of age, it has been administered for prevention of IFD in pediatrics [38, 48, 49]. Posaconazole was first commercialized as oral suspension, but with this, compound treatment was complicated by variable absorption, problem potentially solved by fatty meal and/or other "bundle" measures [50, 51]. Moreover, the use of posaconazole oral solution in patients younger than 13 years has been frequently associated with side effects as rash, abdominal pain, nausea, and vomitus [52]. Tablets containing 100 mg of posaconazole have been approved in 2013 and they show no absorption issue. Furthermore, pediatrics PK/PD data show that the use of this formulation determines effective concentrations also in children [38]. However, tablets are slightly less than 2 cm long and "should be swallowed whole with water and should not be crushed, chewed, or broken" as reported in the "Product Information Document" [53]. Therefore, this approach could not be easy to be applied in children receiving aggressive chemotherapy (mainly for acute myelogenous leukemia or relapsing acute leukemia) because of the presence of mucositis with obvious difficulties in swallowing. Furthermore, this could represent a problem when "a fraction" of a tablet (e.g., 50 mg, 0.5 tablet) is prescribed [38] (Table 1). In this case, a possible trickery could be represented by alternation of the number of tablets (i.e., one a day and two the next day, e.g., 100 mg alternated to 200 mg, in order to obtain a "mean" dose of 150 mg over 2 days) coupled with TDM. When tablets cannot be swallowed but oral therapy is feasible, recent data

Table 1 Primary antifungal prophylaxis in children according to risk levels, evidences, and pharmacological data [22, 38–40]

Risk level	Condition	Prophylaxis[a]
High (≥ 10%)	Acute myeloid leukemia High-risk acute lymphoblastic leukemia Relapsing acute leukemia	Fluconazole: poor evidence to support a recommendation because of the narrow spectrum (yeasts only); dosage: 6 mg/kg per day (maximum 400 mg per day) intravenously or orally q24h Itraconazole: moderate evidence to support a recommendation for use; dosage: oral solution 2.5 mg/kg per day orally (in children aged ≥ 2 years) q12h, with empty stomach. TDM is recommended Posaconazole: oral suspension dosage: 120 mg/m^2 q8h for children who can not swallow tablets. For this formulation a "posaconazole bundle" can be necessary (see Table 2); tablets dosage: loading dose of 300 mg q12h (1st day) then maintenance 300 q24h, independently from meal. A dosage for younger children using tables has been suggested by means of pharmacokinetic studies:
		Body weight / Loading dose (1st day) / Maintenance dose
		> 15–21 kg / 100 mg q12h / 100 mg q24h
		22–30 kg / 150 mg q12h / 150 mg q24h
		31–35 kg / 200 mg q12h / 200 mg q24h
		35–40 kg / 250 mg q12h / 250 mg q24h
		> 40 kg or 13 years old / 300 mg q12h / 300 mg q24h
		TDM is recommended Voriconazole: no evidence to support recommendation; dosage: children aged 2–< 12 years or 12–14 years and weighing < 50 kg 9 mg/kg q12h orally; children aged ≥ 15 years or 12–14 years and weighing ≥ 50 kg: 4 mg/kg q12h (1st day, 6 mg/kg) TDM is recommended Liposomal amphotericin B: intravenous, moderate evidence to support a recommendation for use; dosage 1 mg/kg q24h every other day or 2.5 mg/kg q24h twice weekly; nebulized: no grading, 25 mg q12h on 2 consecutive days per week Micafungin: no grading; dosage: 1 mg/kg (in children weighing ≥ 50 kg, 50 mg) q24h intravenously
Low (≤ 5%)	Acute lymphoblastic leukemia Non-Hodgkin's lymphoma Autologous HSCT	Not recommended
Sporadic	Solid tumors Brain tumors Hodgkin's lymphoma	Not recommended

[a] Prophylaxis for *P. jirovecii* pneumonia should be always considered in all patients' populations

Legend: qxh = every "x" hours; TDM = therapeutic drug monitoring

showed that a dosage of the suspension based on the body surface area allowed to reach effective concentrations too [39]. At present, TDM should be performed for all triazoles (with the possible exclusion of fluconazole) [22, 36, 54] in cancer children receiving antifungal prophylaxis in order to control effectiveness and side effects. Furthermore, TDM with maintenance of adequate plasma concentrations has been associated not only with reduction of adverse events but also in preventing the onset of resistance both in molds and in yeasts [35]. TDM should be considered mandatory for voriconazole in the youngest patients [41, 55–57] and in presence of laboratory signs of inflammation [58–60] or treatment with dexamethasone [61]. For posaconazole, TDM should be considered mandatory if tablets are used in the youngest patients. When changes in dosages are needed because of toxicity or sub-therapeutic plasma levels, specific strategies should be implemented [36, 41] in order to obtain the desired concentrations. Table 2 summarizes target plasma concentrations (trough, C_{min}) and gives some clues for dosages changes and TDM. Triazoles have many interactions with other drugs [54, 62], with the risk of absence of therapeutic effect or adverse events for all the compounds interacting. Sometimes, these interactions signify absolute contraindications for the concomitant use of triazoles with some antineoplastic drugs (e.g., posaconazole and vinca alkaloids that represent a cornerstone for the treatment of acute lymphoblastic leukemia in children). The possibility of drug interactions must always be evaluated any time triazoles are considered for antifungal prophylaxis. Also, in this case, TDM could be very helpful.

Table 2 Triazole plasma trough (C_{min}) concentrations effective for antifungal prophylaxis and strategies to modify dosages in case of low or high serum concentrations. Modified from [36, 41]

Drug	Target trough (C_{min}) concentration and strategies for monitoring	Strategies for dosage modifications in case of low serum concentrations	Strategies for dosage modifications in case of high serum concentrations: empiric changes before plasma concentration available
itraconazole	target concentration for prophylaxis 0.5 mg/L at steady state Measure serum concentrations • 5–7 days after initiation of therapy • following any dose adjustment, • when interacting drugs start or stop • in case of uncertain compliance with oral therapy • in presence of concerns about gastrointestinal absorption • in case of potential clinical or laboratory manifestations of toxicity	Increase total daily dose (e.g., from 200 mg q12h to 300 mg q12h) by 50% and/or • use oral solution (if not already administered) • check if the drug is given in the fasting state • check compliance • s check for top interacting drugs	–
voriconazole	target concentration for prophylaxis > 1 and < 6 mg/L at steady state Measure serum concentrations • before the 5th dose (2 days of treatment), • before the 5th dose following any dose adjustment • routine every 1–2 weeks after achievement of steady-state • when interacting drugs start or stop • in case of uncertain compliance for oral therapy • in case of concerns about gastrointestinal absorption, especially for prolonged periods of time • in case of potential clinical or laboratory manifestations of toxicity	Increase total daily dose by 50% (e.g., from 200 mg q12h to 300 mg q12h), and/or • use a pro/kg dose instead of a fixed one • for patients < 2 years increase dose by 1 mg/kg/day for every 0.5 mg/l rise in trough concentration desired, divided in 3 equal doses • check if the drug is given in the fasting state • check compliance • check for and stop interacting drugs	Withdraw 1 dose, then decrease daily dose by 25% In case of hepathotoxicity • mild-moderate hepatic dysfunction (Child-Pugh score 5–9): start with normal loading dose, reduce maintenance dose by 50% • severe hepatic dysfunction (Child-Pugh score 10–15) do not administer
posaconazole	target concentration for prophylaxis 0.7 mg/L at steady state Measure serum concentrations • 7 days after initiation of therapy • following dose adjustment • when interacting drugs start or stop • in case of uncertain compliance • in case of concerns about gastrointestinal absorption, especially for prolonged periods of time • in case of potential clinical or laboratory manifestations of toxicity	Remove acid suppression if possible (i.e., stop or reduce H_2 antagonists or proton pump inhibitors • check compliance • check for stop interacting drugs For oral solution use check adherence to "posaconazole bundle" • ascorbic acid 500 mg per os with each dose of posaconazole. • 120–180 ml of carbonated soda beverage (i.e., cola or ginger ale) or acidic fruit juice (e.g., cranberry or orange juice) with each dose of posaconazole. • heavy snack or food with each dose, preferably high-fat, including commercially available nutritional supplements.	–

Echinocandins have been less frequently used as antifungal prophylaxis, but they could represent a possible option in order to avoid drug-drug interactions or when oral route is not feasible [22, 23]. Micafungin has an indication for prevention of invasive candidiasis during prolonged neutropenia preceding engraftment in allogeneic HSCT [63]. Caspofungin is not registered for prophylactic use, but it has been demonstrated to be not inferior to liposomal amphotericin B for this indication in allogeneic HSCT patients [64]. No data are available for anidulafungin prophylaxis in children receiving chemotherapy or autologous HSCT. Liposomal amphotericin B (L-AmB) can be another option in children who cannot receive prophylaxis with azoles or echinocandins, but its use could be limited by lack of registration for this indication and clinical trials with adequate power, beyond some severe side effects. A retrospective study demonstrated effectiveness

of intravenous L-AmB administered two times/week compared with historical controls in children with hematologic malignancies [65], and nebulized L-AMB has been administered for IFD prophylaxis in patients with prolonged neutropenia following chemotherapy or allogeneic HSCT [66]. In this last case, efficacy is, obviously, restricted to prevention of pulmonary IFD, and therefore, it should be associated with a drug with systemic effect [22]. Both these class of drugs have no oral formulation forcing the patient to alternative hospitalization (e.g., day-hospital, home care) to receive intravenous prophylaxis.

A last annotation regards correct timing for starting antifungal prophylaxis. This aspect is not well defined, but generally, it is suggested to start together with chemotherapy, or at its end if interacting drugs are used, and to stop it after the resolution of the risk period [21, 22].

Pneumocystis jirovecii Pneumonia

Pneumocystis jirovecii pneumonia (PCP) is a peculiar, severe, life-threatening fungal infection in immunocompromised hosts, both children and adults. The 5th European Conference on Infections in Leukaemia (ECIL-5) provided indications for its prophylaxis in all ages. Trimethoprim/sulfamethoxazole prophylaxis is highly recommended in children affected with acute lymphoblastic leukemia, from induction to end of maintenance, and it is considered optional in acute myelogenous leukemia or solid tumors for all the duration of chemotherapy [67], but should be considered also after autologous HSCT [68]. Prophylaxis is highly effective, and in case of documented failure, especially in adolescents, compliance must be checked [5, 69].

Secondary Antifungal Prophylaxis

Patients with a history of invasive mycosis are at high risk of reactivation when undergoing further aggressive chemotherapy or HSCT (mainly allogeneic). Therefore, secondary antifungal prophylaxis is recommended during aggressive treatments for patients with previous IFD, especially in presence of deep organ localizations. The drug for secondary prophylaxis should be chosen according to the etiology of the primary infection, the localization, the drugs available and their formulations, and the risks of interactions with other therapies, especially those for the treatment of the underlying disease.

Other Prophylactic Measures

Administration of granulocyte (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) has been advocated as a possible prophylactic measure for IFD by reducing duration of neutropenia, but wide studies on their use in pediatrics did not show any effectiveness on mortality [70, 71].

Candida spp. colonize the intestinal tract and the skin, including health workers hands [72–74] that can become vectors for *Candida* colonization and for infections, e.g., by vascular access manipulation. Therefore, correct hands hygiene procedures are an essential practice to reduce also the risk of IFD [75, 76]. Products for hand hygiene containing chlorhexidine gluconate or isopropyl alcohol are more effective in yeast reduction compared to water and soap (4 vs. 50%) [76]. In spite of the low frequency of vascular access-related fungal infections [77, 78], a correct manipulation of these devices performed both in the hospital and at home represents a further aspect for the prevention of IFD [77, 79].

Aspergillus spp. colonization is a necessary condition to develop disease during immunosuppression, and conidia inhalation represents the classical way for acquisition of this pathogen [80]. Inhalation can occur outside the hospital or during hospital admissions, especially during building reconstruction [81, 82]. Use of high-efficiency particulate air (HEPA) filtration, better if associated with positive pressure isolation rather than laminar airflow, could reduce invasive diseases [81], but regular systems inspections and maintenance must be performed [81, 83–86]. Face masks could be utilized too, especially when patients are outside from a hospital room with HEPA filtration or near to building work areas [85], but the use of these devices could be difficult especially in younger children [87]. *Aspergillus* spp. and other filamentous fungi have been found also in hospital water systems [88], which therefore should be periodically controlled. However, there is growing evidence that in many patients, colonization is present before hospitalization, since many of these opportunistic pathogens are present in potted plants, flower arrangements, carpet, and home water supplies [80]. All these conditions should be monitored, and possibly avoided or amended both in the hospital and at patient's home, for an effective program of IFD prophylaxis. These strategies have the advantage of absence of adverse events (if any) and drug interactions, and effectiveness also against other, non-fungal pathogens.

Conclusion

In conclusion, IFD have a high incidence in children receiving aggressive antineoplastic chemotherapy for acute leukemia, but not for solid tumors or undergoing autologous HSCT, even if local epidemiological peculiarities can be present. Mortality is high especially in cases due to molds and in patients at the highest risk. No clinical trial on prophylaxis of IFD with adequate design and power has been performed in children, and many of the pediatric indications are derived

from adults or inferred from pediatric observational studies. In spite of the absence of formal registration for antifungal prophylaxis and/or for the pediatric age, triazoles represent the easiest to use and actually administered drugs for antifungal prophylaxis in children. In any case, the availability of oral formulations and of specific PK/PD pediatric data allows safe and (realistically) effective choices. However, TDM should be considered mandatory for monitoring their effectiveness and safety both in terms of adverse events and resistance selection. Other drugs like echinocandins or L-AmB can be safe and effective, especially in presence of important drug interaction or difficulties in assuming oral drugs, but the lack of an oral formulation reduces their utilization. Finally, non-pharmacological measures as hand hygiene and use of HEPA filters might represent effective and "safe" prophylactic tools not only for the prevention of IFD.

Compliance with Ethical Standards

Conflict of Interest Elio Castagnola has received personal fees from Astellas Pharma and Basilea Pharmaceutica. Alessio Mesini declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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