Antifungal prophylaxis for children with cancer or undergoing haematopoietic stem cell transplant

See also:
Fever and suspected or confirmed neutropenia

In this guideline:

Key points

1. Appropriate antifungal prophylaxis is an important component of cancer care
2. Antifungal prophylaxis has been shown to reduce the risk of invasive fungal infection (IFI) in selected high-risk patients
3. Where possible, an azole agent is preferred and therapeutic drug monitoring should be done for posaconazole, voriconazole and itraconazole.

Background

Children with cancer are at varying risk of invasive fungal infection (IFI). Factors that influence this risk include type of cancer, chemotherapy protocol, depth and duration of neutropenia, steroid exposure and previous history of IFI. Antifungal prophylaxis has been shown to reduce the risk of developing an IFI and can be broadly divided into mould-active (ie. against *Aspergillus* spp.) and non-mould active (ie. against *Candida* spp.) prophylaxis.

Primary antifungal prophylaxis is recommended when the underlying incidence of IFI exceeds 10%. When implementing prophylaxis regimens, consideration must also be given to institutional epidemiology and relevant adjustments made.

Assessment

Prophylaxis recommendations are based on underlying risk of IFI. The type of prophylaxis (mould versus non-mould active) varies according to cancer diagnosis associated complications and/or treatment phases. Patients at high and intermediate risk for IFI should receive appropriate prophylaxis.

Table 1: Stratification of risk of IFI in paediatric cancer/HSCT patients

Risk Stratum	Risk of IFI with	Patient Population
High Risk (≥10%)	**Mould > Yeast**	• High-risk/very-high risk acute lymphoblastic leukaemia (ALL) in intensive treatment phases • Acute myeloid leukaemia (AML) • Relapsed acute leukaemia (ALL and AML) • Allogeneic HSCT with acute Grade II-IV GvHD • Allogeneic HSCT chronic extensive GvHD • Severe aplastic anaemia

	Yeast > Mould	• Allogeneic HSCT (pre-engraftment phase)
Intermediate Risk	**Yeast > Mould**	• Autologous HSCT (neutropenic phase)
Low Risk (≤5%)	-	• Non-relapse ALL (excluding HR & VHR ALL in intensive phases) • Lymphoma (excluding autologous HSCT) • Solid tumours (excluding autologous HSCT)
Sporadic occurrence	-	• Paediatric solid tumours • Brain tumours • Hodgkin's lymphoma

Management

Investigations: Nil

If a patient has a suspected IFI (ie. prolonged or recurrent fever), evaluation and empiric treatment should follow 'Fever and suspected or confirmed neutropenia' CPG.

Primary prophylaxis:

Table 2: Recommended prophylaxis regimens according to patient population (See Table 2 attachment). Refer to Table 3 for dose and monitoring recommendations.

Drug information

Table 3: Antifungal prophylaxis dose, therapeutic drug monitoring (TDM) targets, important food-drug interactions and monitoring recommendations

Antifungal	Dose	Target trough* for prophylaxis	Notes
Fluconazole	6-12 mg/kg (max 400 mg) oral/IV daily oral: round to nearest 50mg capsules	Not routinely required	Administer with or without food Monitor for rash (rare) and hepatotoxicity (rare) Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs Adjust in renal impairment (speak to pharmacy)
Posaconazole	**Oral suspension:** ≥13 years: 200 mg oral TDS **Oral tablets:** ≥13 years OR ≥10 years and ≥30 kgs: 300 mg oral daily	Trough level >0.7 µg/mL Take trough level 5-7 days after starting drug or changing dose or formulation	Administer with food. (absorption ↑with high fat meal) Safety and efficacy in paediatric patients below the age of 13 years has not been well established. Variable doses for posaconazole tablets for children <13 years and <30kg have been described including 200mg oral daily. Discuss with ID and pharmacy if required. Monitor for rash (rare), hepatotoxicity (rare), neurotoxicity and GI upset. Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs Caution in renal impairment as solubilizer may accumulate, consult pharmacy.

Voriconazole	**Oral tablets/suspension:** <2 years: discuss with ID and pharmacy 2 years to <12 years or 12-14 years and weighing <50kg: 9mg/kg (max 350mg) oral BD ≥15 years or aged 12-14 years and weighing ≥ 50kg: 200mg oral BD **Intravenous solution:** <2 years: discuss with ID and pharmacy 2 years to <12 years or 12-14 years and weighing <50kg: 8mg/kg (day 1, 9mg/kg) IV BD ≥15 years or aged 12-14 years and weighing ≥ 50kg: 4mg/kg (day 1, 6 mg/kg) IV BD	Trough level 1-3 µg/mL** Take trough level 5 days after starting drug or changing dose or formulation Dose should not be altered if level is 4-6 mg/L and clinical signs of toxicity are not present	Oral: administer 1 h before or after food (absorption ↓ with high fat meals) Council on avoidance sun exposure. Reports of skin cancer with prolonged (>1yr) use. Caution in renal impairment as IV solubilizer may accumulate. Significance is not known, consult pharmacy. Monitor for rash, hepatotoxicity, neurotoxicity and visual disturbances (NB. a trough level >5-6 is associated with an increased probability of neurological and ocular toxicity). Visual disturbances are dose related, self-limiting and rarely require cessation of therapy. Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs
Itraconazole	**Oral solution (Sporonox®):** 2.5 mg/kg oral BD (max 200 mg daily) **Oral solution and capsules are <u>not</u> interchangeable.** The oral solution is preferred due to improved bioavailability and as there is limited experience with capsules in children. If conversion is required, consult pharmacy.	Trough level >0.5 µg/mL Take trough level 10-15 days after starting drug or changing dose	Liquid (Sporanox®): administer on an empty stomach at least 1h before food. Absorption not affected by H2-anagonists Capsules (Sporanox®): administer with or after food. For patients on gastric acid suppressant medications, separate administration by at least 2 hours and administer with an acidic beverage (e.g. cola). Monitor for rash, hepatotoxicity, neurotoxicity and GI upset. Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs
Liposomal amphotericin (Ambisome®)	2-3mg/kg IV three times per week (**max 100mg daily**) Ambsiome is available in 50mg vials (max 100mg). Where possible round dose to 50mg ensuring dose is at least 2mg/kg (max 100mg).	Not required	Monitor for renal toxicity, electrolyte disturbances (esp hypokalaemia and hypomagnesaemia) and hepatotoxicity. Consider pre/concurrent hydration with 10ml/kg normal saline. Consider premedication if infusion related adverse effects (inc. fever, chills, rigors)
Caspofungin	1 to 3 months: 25mg/m^2 (max 50mg) IV daily ≥3 months: 50mg/m^2 (max 50mg) IV daily	Not required	May cause histamine induced reaction (rash, facial swelling, pruritus and/or bronchospasm)
Micafungin	<4 months age: 2mg/kg IV daily >4 months age: 1mg/kg (max 50mg) IV daily	Not required	May cause histamine induced reaction (rash, facial swelling, pruritus and/or bronchospasm)

*Trough levels for voriconazole, itraconazole and posaconazole are sent to the Alfred hospital and run on a Monday, Tuesday and Thursday (must arrive at The Alfred by 11am). Samples require minimum 1ml in an EDTA tube.
**A voriconazole trough level >5–6 mg/L is associated with an increased probability of neurological toxicity, including visual disturbances, hallucinations and encephalopathy

Therapeutic drug monitoring (TDM)

All patients commenced on itraconazole, voriconazole and posaconazole must have therapeutic drug monitoring (TDM). All patients should have one repeat TDM to confirm stability. Once target trough levels are confirmed, repeat TDM is not routinely required. Indications for repeat TDM include (i) dose or formulation adjustment (ie. iv/oral switch); (ii) introduction of new drug with potential interactions (iii) suspected toxicity (always do level before withholding or adjusting dose); or (iv) diagnosis of a proven, probable or possible IFI.

Depending on the age of the child, azoles may exhibit nonlinear or linear pharmacokinetics. There is also significant INTER- and INTRA- patient variability with these agents. **Dose adjustments should be discussed with oncology pharmacy and/or local infectious diseases unit**. Prior to any dose adjustment, repeat drug level and ensure the following:

Low azole levels	High azole levels
• Confirm true trough sample was taken • Confirm adherence • Exclude poor absorption (absorption reduced with severe mucositis and diarrhoea). Depending on agent, diet may also affect absorption (see Table III) • Investigate potential drug-drug interactions (see below and discuss with pharmacy)	• Confirm a true trough sample was taken • Investigate potential drug-drug interactions (see below and discuss with pharmacy) • If clinical signs of toxicity are not present, consider leaving dose regimen unchanged and monitor potential toxicity carefully.

Secondary prophylaxis

In patients with a documented history of ***proven*** or ***probable*** IFI, secondary prophylaxis is required for further cycles of chemotherapy. The agent that was used to treat the initial infection may be used for prophylaxis, provided it was well tolerated and effective. Discuss with local infectious diseases unit.

Important drug interactions for azole antifungal agents

The azole class of antifungal agents are metabolised by the cytochrome P450 (CYP450) system. The potential for drug-drug interactions is higher for itraconazole and voriconazole than posaconazole and, in particular, fluconazole.

Table IV: Important drug interactions for **azole antifungal agents** and management recommendations.

Medication	Interaction	Management
Decreased plasma concentration of azoles		
Rifampicin, rifabutin	Induces azole metabolism.	Avoid combination where possible. An increase in azole dose may be required
Carbamazepine **Phenobarbitone**	Induces azole metabolism (fluconazole, itraconazole, voriconazole)	
Phenytoin	Induces azole metabolism (itraconazole, voriconazole and posaconazole). Phenytoin metabolism reduced.	Avoid combination where possible. Monitoring of phenytoin and azole levels recommended. An increase in azole dose may be required

Omeprazole and esomeprazole (PO formulations)	Liquid posaconazole: PPI's affect gastric pH and reduce posaconazole liquid absorption and thus levels (less effect on tablets)	Avoid if possible or monitor posaconazole levels.
Increased plasma concentration of co-administered drug		
Vinca alkaloids (vincristine and vinblastine)	Vinca alkaloid metabolism reduced leading to excess vinca alkaloid exposure. Cases of neurotoxicity (peripheral neuropathy, autonomic neuropathy and seizures) have been reported with vincristine and vinblastine and itraconazole, voriconazole and posaconazole. Concurrent use with itraconazole leads to earlier and more severe toxicity. Electrolyte abnormalities, hyponatraemia associated with SIADH and GI upset have also been reported. Fluconazole is a weaker CYP3A4 inhibitor so toxicity is rare.	Concurrent use of itraconazole is strictly contraindicated. Avoid concurrent use of posaconazole where possible (unless advised by infectious diseases and oncology pharmacy) For weekly IV vinca alkaloid: non-azole agent is preferred **For monthly IV vinca alkaloid: withhold voriconazole the day before, the day of and the day after vinca alkaloid dose. Monitor for toxicity**.
Tyrosine kinase inhibitors (TKI): (sorafenib, imatinib, dasatinib, nioltinib, ceritinib, carfizomib, ruxolitinib)	TKI metabolism reduced, increasing risk of toxicity including QT prolongation and cardiac arrhythmias. Refer to chemotherapy protocols for detailed management.	Concurrent use of itraconazole, voriconazole and posaconazole is *not recommended* in most protocols. Fluconazole can be used in most instances *except* in combination with sorafenib. A non-azole agent is mandated for all patients receiving sorafenib.
Venetoclax	Venetoclax metabolism reduced increasing risk of toxicity.	Avoid combination If unavoidable speak to cancer pharmacy and oncology consultant (venetoclax dose reduction may be required)
Bortezomib	Bortezomib metabolism reduced. Cases of new or worsening peripheral neurotoxicity have been reported with itraconazole and voriconazole.	All azoles should be stopped 72 hours prior to bortezomib dosing and recommenced 72 hours (24 hours for fluconazole) after final dose in course. A non-azole agent should be substituted during this period. For example, in patients with AML receiving bortezomib on D1 and D8 in a 28-day curse, substitute voriconazole or posaconazole for an echinocandin on D(-3) to D(+3)
Busulfan, Thiotepa	Metabolism reduced (CYP3A4), leading to significant increases in levels of these drugs.	Avoid voriconazole, posaconazole or itraconazole 7 days prior to starting HSCT conditioning (not fluconazole)
Proton pump inhibitors (omeprazole and esomeprazole)	Reduced metabolism of voriconazole (CYP2C19), increasing voriconazole levels	Monitor voriconazole levels and signs of toxicity. In particular when starting or stopping the PPI.
Sirolimus, Tacrolimus, Cyclosporin, Everolimus and Temsirolimus	Metabolism reduced, leading to significant increases in levels of these drugs. Reports of significantly increased trough concentrations despite dose reduction, due to combination of itraconazole and sirolimus.	Monitor sirolimus, tacrolimus or cyclosporine levels. Dose reduction usually required. Itraconazole should be used with extreme caution in patients on sirolimus.
Diazepam, midazolam	Metabolism reduced, increasing risk of toxicity including respiratory depression	Monitor for signs of toxicity
Prolonged QT interval		
Gemtuzumab and macrolide & quinolone antibiotics,	Additive risk of QT prolongation in setting of azole prophylaxis	Use combination in caution. Obtain an ECG prior to starting treatment and weekly thereafter. Azoles should not be used in patients with additional cardiac risk factors including reduced left ventricular fraction and electrolyte disturbances.

conventional antipsychotics		

Consider consultation with local paediatric team when:
All decisions to start and stop antifungal prophylaxis as well as issues with tolerability or side effects should be discussed with the patients primary treating team.

Consider transfer when:
All suspected or confirmed fungal infections should be discussed with the patients primary treating team and consideration given to transfer to a tertiary paediatric cancer centre for investigation and management.

References

Lehrnbecher T et al. Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients. J Clin Oncol. 2020 Sep 20;38(27):3205-3216

Boonsathorn S. Clinical Pharmacokinetics and Dose Recommendations for Posaconazole in Infants and Children. Clin Pharmacokinet. 2018

Chau MM et al. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2014. Intern Med J. 2014; v44

Fleming S et al. Consensus guideline for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation*, Intern Med J.* 2014;44(12b):1283-97

Maertens JA et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother. 2018

Tragiannidis A et al. Plasma explosure following posaconazole delayed release tablets in immunocompromised children and adolescents. J Antimicob Chemother. 2019