Guideline

Antifungal Prophylaxis and Treatment in Paediatric Oncology Patients and other Immunocompromised Children

Document ID	CHQ-GDL-01075	**Version no.**	4.1	**Approval date**	28/04/2022
Executive sponsor	Executive Director of Medical Services			**Effective date**	10/04/2024
Author/custodian	Director of Infection Management and Prevention service, Immunology and Rheumatology			**Review date**	09/10/2024
Supersedes	4.0				
Applicable to	All Children's Health Queensland (CHQ) clinical staff				
Authorisation	Executive Director Clinical Services				

Purpose

This Guideline provides recommendations regarding best practice for Antifungal Prophylaxis and Treatment in paediatric oncology patients and other immunocompromised children.

Scope

This Guideline provides information for Children's Health Queensland (CHQ) staff caring for paediatric oncology patients and other immunocompromised children.

Related documents

- CHQ-GDL-0129 Management of Fever in a Paediatric Oncology Patient- Febrile Neutropaenia and Febrile Non-neutropaenia
- CHQ-PROC-01036 Antimicrobial: Prescribing and Management
- CHQ Antimicrobial Restriction list

Contents

- Table 4: Paediatric Posaconazole dosing and TDM recommendations
- Table 5: Antifungal pharmacokinetics and dosing in infants and children on Extracorporeal Membrane Oxygenation (ECMO)
- Table 6: Important drug interactions for azole antifungal agents

Antifungal Prophylaxis and Treatment in Paediatric Oncology patients and Immunocompromised Children Guideline

Summary of prophylaxis options (Table 1)

(1) Fluconazole is appropriate prophylaxis in patients at low risk of mould infections

(2) Voriconazole, posaconazole micafungin, or liposomal amphotericin B (Ambisome®) are all potential options in patients who are at high risk of a mould infection. There is no data to prove superiority of one agent over the others. Therefore, local practice should take into consideration individual patient circumstances, Pharmaceutical Benefit Scheme (PBS) approved indications, ease of administration and cost.

Primary antifungal prophylaxis:

Risk for invasive fungal infection (IFI) varies by treatment regimen and underlying diagnosis. Additionally, distinguishing the risk for candida infection versus mould infection warranting anti-mould prophylaxis informs decisions around antifungal choice. Posaconazole Modified Release (MR) tablets are listed on the Pharmaceutical Benefit Scheme (PBS) for antifungal prophylaxis against yeasts and moulds, and this guideline therefore recommends posaconazole as first line in children over 8 years where anti-mould prophylaxis is required. With uncertainties around dosing and variable absorption in younger children with posaconazole, voriconazole is the preferred choice in children under 8 years of age.

Secondary antifungal prophylaxis:

Risk of subsequent IFI after probable or proven fungal infection remains high. Antifungal therapy should be continued as secondary prophylaxis for duration of each neutropenic episode, until neutropenia has resolved and patient is no longer immunosuppressed.

Timing and duration of antifungal prophylaxis:

Most studies commence prophylaxis during administration of chemotherapy or estimated 3 days before neutrophils expected to fall to less than 0.5x10^9/L. Cessation is generally recommended following resolution of risk, which in acute leukaemia corresponds with neutrophil reconstitution (more than 1.0 × 10^9/L).

ALERT

NOTE: Duration of voriconazole prophylaxis

If voriconazole prophylaxis (primary or secondary) is necessary for longer than 6 months, in view of the risk of photosensitivity (and recent rare reports of skin malignancies and fluorosis) it may be appropriate to consider switching to another azole, either itraconazole or posaconazole. This should be a consultant-led decision based on the individual patient's clinical circumstances.

Summary of treatment options (Table 2)

Empirical anti-fungal therapy in the context of febrile neutropaenia

Febrile neutropenia prolonged fever (more than 96 hours) add:

- Liposomal Amphotericin (Ambisome®) IV 1 mg/kg once daily and assess as per FN protocol. (CHQ-GDL-01249 Management of Fever in a Paediaric Oncology Patient - Febrile neutropenia (FN) and Febrile Non-neutropenia protocol.)

Treatment of possible, probable and proven fungal infection (discuss with Oncology and Infection Management) (See Table 2)

Key considerations: When a yeast or mould is isolated from a sterile site request microbiology lab perform sensitivity testing.

Switch to oral therapy (voriconazole/ posaconazole / fluconazole) when no azole drug contraindications, afebrile, clinically stable, tolerating oral feeds and able to maintain therapeutic levels.

Duration of treatment is tailored to individual patients, underlying diagnosis and pathogen but is generally 4 to 12 weeks.

ALERT

Liposomal Amphotericin (Ambisome®) to oral azole switch does not require routine establishment of therapeutic azole levels before stopping Ambisome®.

Table 1: Risk stratification: Prophylaxis for invasive fungal infection (IFI) in high risk patient groups

Disease	Specific subgroup	Timing of prophylaxis	Recommended prophylaxis		Alternative if recommended agent contraindicated (eg weekly vincristine or tyrokinase inhibitor)
			Under 8 years old	**8 years and older**	**All ages**
ALL (note: if on immunotherapy treatment or shorter steroid courses, mould active prophylaxis may not be required at SMO oncologist discretion)	**Relapsed ALL**	Start: with relapse diagnosis	<1 years of age: Itraconazole PO >1 years of age: Voriconazole PO Alternative: Posaconazole PO	Posaconazole PO Alternative: Voriconazole PO	Micafungin IV – daily (inpatient) Micafungin IV – three times a week (HITH) Alternative: Ambisome ®IV
	Infant ALL (< 1 year old at diagnosis) **VHR/ T-cell ALL** **HR ALL (induction only)**	Start: when ANC < 1.0 and during intensive phase only (induction, consolidation and delayed intensification) Stop: when ANC is ≥1.0 for at least 7 days			
	HR ALL consolidation / delayed intensification		Fluconazole PO	Fluconazole PO	Micafungin IV – daily (inpatient) Micafungin IV – three times a week (HITH)
	SR ALL	Routine prophylaxis not recommended unless mandated by trial protocol			
AML (note: mould active prophylaxis may not always be required for Downs syndrome protocols.)	**Relapsed AML**	Start: with relapse diagnosis	Voriconazole PO Alternative: Posaconazole PO	Posaconazole PO Alternative: Voriconazole PO	Micafungin IV – daily (inpatient) Micafungin IV – three times a week (HITH) Alternative: Ambisome ®IV
	AML **Infant AML**	Start: following last dose of chemotherapy in cycle or ANC<1.0 Stop: when ANC is ≥1.0 for at least 7 days			
Aplastic anaemia	**Severe aplastic anaemia (while neutropenic < 0.5)**	Start when neutrophil count is less than 0.5	Voriconazole PO Alternative: Posaconazole PO	Posaconazole PO Alternative: Voriconazole PO	Micafungin IV – daily (inpatient) Micafungin IV – three times a week (HITH) Alternative: Ambisome ®IV
Allogeneic HSCT	**Low risk**	Start during conditioning	Fluconazole PO/IV		
	High risk	Start during conditioning	Ambisome ® IV– daily		Alternative: Micafungin IV - daily
		Switch as per HSCT protocol / when tolerating oral Stop: day + 100	Voriconazole PO	Posaconazole PO	

Table 1: Risk stratification: Prophylaxis for invasive fungal infection (IFI) in high risk patient groups (continued)

Disease	Specific subgroup	Timing of prophylaxis	Recommended prophylaxis		Alternative if recommended agent contraindicated
			Under 8 years old	**8 years and older**	**All ages**
Allogeneic HSCT	**With GvHD requiring prolonged systemic steroid therapy**	Start at GvHD diagnosis Stop: when corticosteroid dose is < 0.5mg/kg or 10 mg daily prednisolone equivalent (whichever is less).	Voriconazole PO Alternative: Posaconazole PO	Posaconazole PO Alternative: Voriconazole PO	Liposomal Amphotericin (Ambisome ®) IV– daily Alternative: Micafungin IV – daily (inpatient) Micafungin IV – three times a week (HITH)
Autologous HSCT	**Pre-engraftment phase**	Start: during conditioning Stop: when ANC is ≥1.0 for at least 7 days	Fluconazole PO	Fluconazole PO	Micafungin IV – daily Micafungin IV – three times a week (HITH)
Neuroblastoma	**Stage 4 Neuroblastoma**	Start: with or just after chemotherapy is commenced. Stop: when ANC is ≥1.0 for at least 7 days	Fluconazole PO	Fluconazole PO	Micafungin IV – daily Micafungin IV – three times a week (HITH)
Langerhans Cell Histiocytosis (LCH)	**LCH Induction therapy**	Start: with or just after chemotherapy is commenced. Stop: when ANC is ≥1.0 for at least 7 days	Fluconazole PO	Fluconazole PO	Micafungin IV – daily Micafungin IV – three times a week (HITH)
Lymphoma	**Excluding patients undergoing any HSCT**	Routine prophylaxis not recommended			
Solid tumours (receiving chemotherapy)		Routine prophylaxis not recommended			

Table 1: Risk stratification: Prophylaxis for invasive fungal infection (IFI) in high risk patient groups (continued)

Disease	Specific subgroup	Timing of prophylaxis	Recommended prophylaxis		Alternative if recommended agent contraindicated
			Under 8 years old	**8 years and older**	**All ages**
Primary immune deficiency with a high risk of IFI **As directed by Immunology SMO**	**Severe combined immunodeficiency (SCID)**	Start at time of diagnosis	Fluconazole PO		Seek ID advice
	DiGeorge Syndrome (severe disease)	Start at time of diagnosis			
	Chronic mucocutaneous candidiasis				
	Hyper IgE syndromes				
	Chronic granulomatous disease (CGD)	Start at time of diagnosis	Itraconazole PO Alternative: Voriconazole PO Itraconazole PO	Itraconazole PO Alternative: Posaconazole PO	
	Wiskott-Aldrich Syndrome (classic, severe) (WAS)	As per immunology SMO			
	Severe phagocyte defects eg congenital neutropaenia, LAD	As per immunology SMO			

Table 2. Treatment of suspected or proven fungal infection (discuss with Oncology and IMPS)

Indication	Antifungal choice	Comment
Empirical Treatment*		
Febrile neutropenia prolonged fever (more than 96 hours)	Add Liposomal Amphotericin (Ambisome ®) IV 1 mg/kg once daily	Assess as per CHQ Febrile neutropenia (FN) protocol.
Invasive fungal infection (IFI) treatment (probable or possible, no organism identified)	Ambisome ® IV 3 mg/kg once daily; followed by Voriconazole PO	
IFI with CNS disease suspected (no organism identified)	Voriconazole IV	
Disseminated Candidiasis / candidaemia	First line: Echinocandins# (Caspofungin IV) Alternatives: Voriconazole; Ambisome® IV	Tailor to pathogen once spp and sensitivities
Candida Pyelonephritis / complicated UTI	Fluconazole IV/oral Alternatives: Ambisome® IV	Neither echinocandins nor voriconazole concentrate well in urine.
Microbiologically Directed Treatment* (tailored individually to child and pathogen**)**		
Candida albicans	First line: Fluconazole Alternatives: Caspofungin IV#, Voriconazole, Ambisome ® IV	Can be used for infections due to *C tropicalis, C kefyr, C dubliniensis, C lusitaniae,* and *C guilliermondi*.
Candida glabrata	First line: Caspofungin IV # Alternatives: Voriconazole, Ambisome® IV. Fluconazole (only if sensitivity confirmed)	
Candida krusei	First line: Caspofungin IV # Alternatives: Posaconazole, Voriconazole	
Candida parapsilosis	First line: Fluconazole Alternatives: Voriconazole, Ambisome® IV, Caspofungin IV#	Echinocandins have higher MICs against *Candida parapsilosis* group; however, no diminished efficacy against these species has been noted in randomised clinical trials
Aspergillus spp	First line: Voriconazole Alternative: Ambisome® IV	
Aspergillus terreus	Voriconazole	Resistant to amphotericin
Lomentaspora / Scedosporium	First line: Voriconazole and Terbinafine Alternative: Posaconazole	
Fusarium	Ambisome® (5 mg/kg IV once daily) and Voriconazole IV	
Mucormycoses	First line: Ambisome® (5 mg/kg to 7.5 mg/kg IV once daily) Alternative: Posaconazole	

*See Table 3 and 4 for dosing and monitoring recommendations.

#Echinocandins: There are more dosage and safety data for caspofungin and micafungin than anidulafungin in children and for micafungin in neonates and infants. Anidulafungin has no significant drug interactions at all and requires less dose adjustment with moderate to severe liver disease, but is approved for adults only. Choice of echinocandin depends on age of child, potential drug interactions, type of infection and comorbidities as advised by IMPS.

Table 3: Dosing and therapeutic drug monitoring (TDM) recommendations for antifungals (normal renal and hepatic function) – prophylaxis and treatment

Antifungal	Prophylaxis	Treatment	TDM	Comments
Liposomal Amphotericin B (Ambisome ®)	**Infants, children and adolescents:** 3 mg/kg IV three times per week (Mondays, Wednesdays and Fridays of each week) (Max 100 mg/dose) **OR** **1 mg/kg/IV daily (Max 100 mg/dose)** **Neonates:** Limited data. Seek ID specialist advice.	**Infants, children and adolescents:** 3 mg/kg to 5 mg/kg IV once daily **CNS disease/meningitis:** 5 mg/kg to 7.5 mg/kg IV once daily on advice from ID specialist **Neonates:** Limited data. Seek ID specialist advice. (Conventional amphotericin B (Fungizone®) preferred in neonates) **Obesity:** For patients weighing more than 100 kg, fixed dosing is recommended. 3 mg/kg IV daily (Max 300 mg/day) and seek specialist advice 5 mg/kg IV daily (Max 500 mg/day) and seek specialist advice.	Not required	Dose based on actual body weight. For patients weighing more than 100 kg, fixed dosing is recommended. See treatment dosing recommendations. Monitor for renal toxicity, electrolyte disturbances (especially hypokalaemia and hypomagnesaemia) and hepatotoxicity. Consider premedication if infusion related adverse effects (inc. fever, chills, rigors)
Anidulafungin	**Infants, children and adolescents:** 1.5 mg/kg IV once daily (Max 100mg/day) **Neonates:** Limited data. Seek ID specialist advice.	**Infants, children and adolescents:** **Loading dose:** 3mg/kg IV as a single dose on day 1 (Maximum 200 mg/day) **Maintenance dose:** 1.5 mg/kg IV once daily from day 2 onwards (Maximum 100 mg/day) **Neonates:** Limited data. Seek ID specialist advice.	Not required	No dose adjustment for renal or liver impairment. Obesity: Increase daily dose by 25-50% of the usual dose in patients weighing >75 kg.
Caspofungin	**Infants (>3 months), children and adolescents:** 50 mg/m2 IV daily (Maximum 50 mg/day) **1 to 3 months of age:** 25 mg/m2 IV daily (Maximum 25 mg/day) **Neonates:** Limited data. Seek ID specialist advice.	**Infants (>3 months), children and adolescents:** **Loading dose:** 70 mg/m2 IV on day 1 (Maximum 70 mg/day) **Maintenance dose:** 50 mg/m2 IV on day 2 onwards (Maximum 50 mg/day) **In critically ill patients**, maintenance dose can be increased to 70 mg/m2/day (maximum 70 mg/day) **1 to 3 months of age:** 25 mg/m2 IV daily (Maximum 25 mg/day) **Neonates:** Limited data. Seek ID specialist advice.	Not required	May cause histamine induced reaction (rash, facial swelling, pruritus and/or bronchospasm). Monitor for hepatotoxicity and electrolyte disturbances (especially hypokalaemia, hypercalcaemia and hypomagnesaemia) and hepatotoxicity. No dose adjustment for renal impairment. Hepatic impairment: For Child-Pugh score of 7-9 (class B; significant functional compromise), after loading dose, reduce maintenance dose by 50%. Obesity: Increase daily dose by 25-50% of the usual dose in patients weighing >75 kg.

Table 3: Antifungal paediatric dosing and therapeutic drug monitoring (TDM) recommendations (normal renal and hepatic function) – prophylaxis and treatment (CONTINUED)

Antifungal	Prophylaxis	Treatment	TDM	Comments
Fluconazole	**Infants, children and adolescents:** 6 mg/kg (maximum 400 mg) oral/IV once daily **Term Neonates:** **Week 1 of life:** 3 mg/kg/dose to 6 mg/kg/dose oral/IV twice weekly **Week 2 to 4 of life:** 6 mg/kg/dose oral/IV every 72 hourly	**Infants, children and adolescents**: **Loading dose:** 12 mg/kg (maximum 800 mg) IV/oral as a single dose **Maintenance dose:** 6 mg/kg (maximum 400 mg) IV/oral once daily Use 12 mg/kg (maximum 800 mg) IV/oral once daily if Immunocompromised or infection is severe **Term Neonates:** **Loading dose:** 25 mg/kg IV as a single dose **Maintenance dose:** **Week 1 of life:** 12 mg/kg IV/oral every 48 hourly **Week 2 to 4 of life:** 12 mg/kg IV/oral once daily	Not routinely required. Advisable for patients with severe IFI, on CRRT or ECMO. Seek ID specialist advice. An AUC/MIC ratio ≥ 50 for Candida species with MIC breakpoint ≤ 8 mg/L corresponds with a favourable outcome, requiring an AUC of ≥400 mg × h/L. a Higher AUC target of 800 mg × h/L in immunocompromised and critically ill patients with invasive Candida may be preferred.	Obesity: Dose based on total body weight. Administer with or without food Monitor for rash (rare) and hepatotoxicity (rare) Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs Drug interactions (see Table 5)
Flucytosine	Seek ID advice.	Administer in combination with susceptible antifungal due to development of resistance. Seek ID advice. **Infants, children and adolescents:** 25 mg/kg oral every 6 hourly **Term Neonates:** Week 1 of life: 25 mg/kg oral every 8 hourly Week 2 to 4 of life: 25 mg/kg oral every 6 hourly	Take trough (30 minutes pre-dose) and peak level (2 hours post dose) on day 3 after starting drug or changing dose **Treatment:** Trough level: 25 to 50 mg/L Peak level: 50 to 100 mg/L Bone marrow and hepatotoxicity associated with peak levels exceeding 100 mg/L	Dose based on ideal body weight. Monitor FBC, renal and liver function closely (daily initially, then twice a week) Renal impairment – dose adjustment required if CrCl <40 mL/min Hepatic impairment – seek ID specialist advice.

Table 3: Antifungal paediatric dosing and therapeutic drug monitoring (TDM) recommendations (normal renal and hepatic function) – prophylaxis and treatment (CONTINUED)

Antifungal	Prophylaxis	Treatment	Therapeutic drug monitoring	Comments
Itraconazole	**Oral solution (Sporanox®):** **1 month to <12 years:** 5 mg/kg oral twice daily (maximum 200 mg/dose) **Neonates:** Limited data. Seek ID specialist advice. **Oral capsules (Sporanox ®): 12 to 18 years:** 2.5 mg/kg oral twice daily (maximum 200 mg/dose) Oral solution and capsules are not 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.		Take trough level on day 7 to 10 after starting drug or changing dose **Prophylaxis:** Trough level ≥500 to 1000 microgram/L* **Treatment:** Trough level 1000 to 2000 microgram/L*	Liquid (Sporanox®): administer on an empty stomach at least 1 hour before food with an acidic beverage (e.g. cola, orange juice) 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, orange juice) Monitor for rash, hepatotoxicity, neurotoxicity and GI upset. Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs. Drug interactions (see Table 5) *Itraconazole levels measured using HPLC method
Micafungin	**Infants, children and adolescents:** **Inpatient:** 1 mg/kg IV daily (Max 100 mg/day) **HITH:** 3 mg/kg IV three times a week (Max 200 mg/dose) **Neonates:** Limited data. Seek ID specialist advice.	**Infants and children up to 2 years:** 5 mg/kg IV once daily (Max 100 mg/day) **2 to 16 years (up to 40kg):** 3 mg/kg IV once daily (Max 100 mg/day*) **16 to 18 years (more than 40kg):** 3mg/kg IV once daily (Max 150 mg/day) (* Increase to maximum 200 mg once daily if response is inadequate) **Term Neonates:** General: 4 mg/kg IV once daily CNS infection: 10 mg/kg IV once daily	Not required	May cause histamine induced reaction (rash, facial swelling, pruritus and/or bronchospasm) Obesity: Increase daily dose by 25-50% of the usual dose in patients weighing >75kg. No dose adjustment for renal or hepatic impairment.
Posaconazole	**See table 4.**			

Table 3: Antifungal paediatric dosing and therapeutic drug monitoring (TDM) recommendations (normal renal and hepatic function) – prophylaxis and treatment (CONTINUED)

Antifungal	Prophylaxis	Treatment	TDM	Comments
Voriconazole	Optimal dosing for prophylaxis is not established. Australian guidelines recommend using the same doses as for treatment. **Infants and children up to 2 years:** 9 mg/kg oral twice daily **2 to 12 years (up to 50 kg):** **Loading dose:** 9 mg/kg oral twice daily for 2 doses (maximum 350 mg/dose) **Maintenance dose:** 8 mg/kg oral twice daily (maximum 200 mg/dose) **12 to 15 years (less than 50 kg):** **Use dose for children 2 to 12 years (above)** **12 to 15 years (more than 50 kg):** **Use dose for adolescents 15 to 18 years (below)** **15 to 18 years (more than 50 kg):** **Loading dose:** 6 mg/kg oral twice daily for 2 doses (maximum 400 mg/dose) **Maintenance dose:** 4 mg/kg oral twice daily (maximum 200 mg/dose) **Neonates:** Limited data. Seek ID specialist advice.	**Infants and children up to 2 years:** 9 mg/kg IV/oral twice daily **2 to 12 years (up to 50 kg):** **Loading dose:** 9 mg/kg IV/oral twice daily for 2 doses **Maintenance dose- Intravenous:** 8 mg/kg IV twice daily and titrate according to TDM results. **Maintenance dose - Oral:** 9 mg/kg oral twice daily (maximum initial dose of 350 mg/dose then titrate according to TDM results) **12 to 15 years (less than 50 kg):** **Use dose for children 2 to 12 years (above)** **12 to 15 years (more than 50 kg): Use dose for adolescents 15 to 18 years (below)** **15 to 18 years (more than 50 kg):** **Loading dose:** 6 mg/kg IV/oral twice daily for 2 doses **Maintenance dose- Intravenous:** 4 mg/kg IV twice daily and titrate according to TDM results. **Maintenance dose- Oral:** 4 mg/kg oral twice daily (maximum initial dose of 200 mg/dose then titrate according to TDM results). **Neonates:** Limited data. Seek ID specialist advice.	**Prophylaxis:** *Timing:* Trough level on day 5 *Target:* Trough level 1 to 2 mg/L **Treatment:** *Timing:* Take trough level (30 minutes pre-dose) before 4th dose as a safety check. If level > 4 mg/L, contact ID/ Oncology consultant to discuss dose adjustment. Repeat trough level on day 5 (steady state) after starting drug or changing dose. *Target:* Trough level 1 to 5 mg/L A higher target (e.g. >2 mg/L) should be used if there is disease with a poor prognosis (e.g. CNS infection, bulky disease, multifocal infection) Note: a trough level of more than 5 or 6 mg/L is associated with an increased probability of neurological and ocular toxicity.	Administer 1 hour before or after food (absorption reduced with high fat meals). Council on avoidance sun exposure. Reports of skin cancer with prolonged (more than 6 months) use. Concurrent omeprazole may increase IV voriconazole levels (boosting via CyP 2C19 interaction). Monitor for rash, hepatotoxicity, neurotoxicity and visual disturbances. 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. Obesity: Dose based on adjusted body weight. Caution in renal impairment as solubilizer (SBECD) may accumulate. Significance is not known, consult pharmacy. In mild to moderate hepatic impairment (Child-Pugh score of 7 to 9; class B - significant functional compromise, after loading dose, reduce maintenance dose by 50% and perform therapeutic drug monitoring. Drug interactions (see Table 5)

Table 3: Antifungal paediatric dosing and therapeutic drug monitoring (TDM) recommendations (normal renal and hepatic function) – prophylaxis and treatment (CONTINUED)

Antifungal	Prophylaxis	Treatment	TDM	Comments
Terbinafine	Not routinely used for prophylaxis	**Infants, children and adolescents:** **Weight banded dosing:** 10 to 20 kg: 62.5 mg orally once daily 20 to 40 kg: 125 mg orally once daily More than 40 kg: 250 mg once daily **Life threatening infection (for example Scedosporium/ Lomentaspora, high dose terbinafine used in combination with voriconazole):** **Seek ID advice.** 10 to 20 kg: 125 mg orally once daily 20 to 40 kg: 250 mg orally once daily More than 40 kg: 500 mg once daily (Dolton M et al. AAC. 2014; 58 (1): 48-54) **Neonates:** Limited data. Seek ID specialist advice.	Not currently available in Australia.	Take doses with or without food. Monitor for rash, hepatotoxicity and bone marrow toxicity. Disturbances of taste/smell may occur; resolution may be delayed (>1 year) following discontinuation of terbinafine, or in rare cases may be permanent. Renal impairment – dose adjustment required if CrCl less than 50 mL/min. Hepatic impairment – in hepatic cirrhosis, terbinafine clearance is decreased by 50%. Seek ID specialist advice.

Table 4: Paediatric Posaconazole dosing and Therapeutic drug monitoring (TDM) recommendations:

Age group, years	Initial prophylaxis dose	Prophylaxis dose increase if trough level < 0.5 mg/L	Initial treatment dose	Treatment dose increase if trough level < 1 mg/L	Comments
Posaconazole Oral suspension (Administer with food - absorption increased with high fat meal)					
6 months to <2 years	200 mg orally THREE times a day	Consider increase to 200 mg orally FOUR times a day	200 mg orally FOUR times a day	Seek ID advice	**All formulations:** **Therapeutic drug monitoring:** Trough level (30 minutes pre-dose) on day 5 to 7 after starting drug or changing dose **Prophylaxis**: trough ≥ 0.5 to 0.7 mg/L **Treatment:** trough 1 to 3 mg/L Avoid antacids, H2 receptor antagonists, proton pump inhibitors. Monitor for rash (rare), hepatotoxicity (rare), neurotoxicity and GI upset. Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs. No dosage adjustment in renal impairment. Intravenous vehicle may accumulate. Severe hepatic impairment: Seek ID advice. Avoid unless risk/benefit has been assessed. **Additional notes - IV Posaconazole:** Not licensed in children <18 years of age. Drug interactions (see Table 5)
2 to 6 years	200 mg orally THREE times a day	Consider increase to 200 mg orally FOUR times a day	200 mg orally FOUR times a day	Consider increase to 300mg orally FOUR times per day	
7 to 16 years (and unable to swallow tablets)	300 mg orally THREE times a day	Consider increase to 300 mg orally FOUR times a day	300 mg orally FOUR times a day	Consider increase to 400mg orally FOUR times per day	
Posaconazole Modified release tablets (Swallow tablets whole – do not crush/chew. Administer with food or without food)					
7 to 16 years (>30kg and able to swallow tablets)	300 mg orally once daily	Seek ID advice	**Loading dose:** **Day 1:** 300 mg orally twice daily for 2 doses **Maintenance dose:** **Day 2 onwards:** 300 mg orally once daily	Seek ID advice	
Posaconazole Intravenous solution					
1 to 18 years	Seek ID advice	Seek ID advice	**Loading dose:** **Day 1:** 10 mg/kg IV twice daily for 2 doses (Max 300 mg/dose) **Maintenance dose:** **Day 2 onwards:** 10mg/kg IV once daily (Max 300mg/day)	Seek ID advice	

Azole Therapeutic drug monitoring (TDM)

Itraconazole, voriconazole and posaconazole require 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:

- Dose adjustment or IV to Oral switch
- Introduction of new drug with potential interactions
- Suspected toxicity (always do level before withholding or adjusting dose)
- Prolonged febrile neutropenia (>96 hours) (to ensure antifungal levels are therapeutic)
- 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 Senior pharmacist and/or ID specialist.

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 3) Investigate potential drug-drug interactions (see below and discuss with pharmacy)	Confirm a true trough sample was taken Investigate potential drug-drug interactions (see Table 5 and discuss with pharmacy) If clinical signs of toxicity are not present, consider leaving dose regimen unchanged and monitor potential toxicity carefully.

Fluconazole therapeutic drug monitoring is not routinely required.

- Advisable for patients with severe IFI, on CRRT or ECMO. Seek ID specialist and Senior pharmacist advice.
- An AUC/MIC ratio ≥ 50 for Candida species with MIC breakpoint ≤ 8 mg/L corresponds with a favourable outcome, requiring an AUC of ≥ 400 mg × h/L.
- a Higher AUC target of 800 mg × h/L in immunocompromised and critically ill patients with invasive Candida may be preferred.

Table 5: Antifungal pharmacokinetics and dosing in infants and children on Extracorporeal Membrane Oxygenation (ECMO)

In addition to pharmacokinetic changes, other considerations for dosing whilst patients are on ECMO:

- Degree of lipophilicity of drug
- Type of ECMO (VV vs VA ECMO, with/without haemofiltration/ SCUF)
- Priming volume/haemodilution
- Adsorption to OR sequestration of drug by the circuit (eg, increased lipophilicity: Expect considerable loss in the ECMO circuit)
- Recirculation

Antifungal dosing in ECMO is complex, individualised and requires specialist ECMO pharmacist advice**

Antifungal	Volume of distribution compared to non-ECMO patients	Clearance compared to non-ECMO patients	Dosing suggestions for infants and children on ECMO**	Comments
Anidulafungin	Unchanged	Unchanged	**Infants, children and adolescents:** **Loading dose:** 3 mg/kg IV as a single dose on day 1 (Maximum 200 mg/day) **Maintenance dose:** 1.5 mg/kg IV once daily from day 2 onwards (Max 100 mg/day)	No paediatric ECMO data. One adult case report. Use standard dosing (Table 2) and seek ID specialist advice No TDM available
Liposomal Amphotericin B (Ambisome)	Unchanged	Unchanged	**Infants, children and adolescents:** 3 mg/kg to 5 mg/kg IV once daily **CNS disease/meningitis:** 5 mg/kg to 7.5 mg/kg IV once daily on advice from ID specialist.	No paediatric ECMO data. Use standard dosing (Table 2) and seek ID specialist advice No TDM available
Caspofungin	Increased	Increased	**Infants, children and adolescents:** 70 mg/m2 IV once daily (Maximum 70 mg/day) and seek ID specialist advice.	No paediatric ECMO data. Conflicting reports in the literature. Minimal to moderate circuit drug sequestration. Dose adjustments may be required. No TDM available.
Fluconazole	Increased	Unchanged	**Prophylaxis:** **Loading dose:** 12 mg/kg IV as a single dose, **Maintenance dose:** 6 mg/kg IV once daily (Max 400 mg/day) **Treatment:** **Loading dose:** 35 mg/kg IV as a single dose, **Maintenance dose:** 12 mg/kg IV once daily (Max 800 mg/day)	Studies reviewed PKPD in infants on ECMO. Higher loading dose recommended. Perform therapeutic drug monitoring – seek ID specialist and Senior pharmacist advice. a Higher AUC target of 800 mg × h/L in immunocompromised and critically ill patients with invasive Candida may be preferred.

Table 5: Antifungal pharmacokinetics and dosing in infants and children on Extracorporeal Membrane Oxygenation (ECMO) (CONTINUED)

Antifungal	Volume of distribution compared to non-ECMO patients	Clearance compared to non-ECMO patients	Dosing suggestions for infants and children on ECMO**	Comments
Micafungin	Increased	Increased/ Unchanged	**Infants, children up to 2 years:** 5 mg/kg IV once daily (Maximum 100 mg) **2 to 16 years (up to 40 kg):** 3 mg/kg IV once daily (Maximum 100 mg/day) **16 to 18 years (more than 40 kg):** 3 mg/kg IV once daily (Maximum 200 mg/day*) (*if response is inadequate)	Clearance and Vd higher in infants Drug is minimally sequestered in ECMO circuit (Sanchez et al, ECCMID 2016) No TDM available
Posaconazole	Increased	Increased	**Intravenous:** **Loading dose:** 10 mg/kg IV twice daily for 2 doses (Maximum 300 mg/dose) **Maintenance dose:** 10 mg/kg IV once daily (Maximum 300 mg/day)	Early sequestration on ECMO circuit which may result in difficulties achieving therapeutic levels early on. Perform therapeutic drug monitoring early and repeat regularly (every 48- 72 hours initially) – seek ID specialist/ pharmacist advice.
Voriconazole	Increased	Decreased	**Intravenous: Loading dose:** 14 mg/kg IV twice daily for 2 doses (Maximum 400 mg/dose) **Maintenance dose:** 8 to 9 mg/kg IV twice daily and adjust according to TDM (Maximum 300 mg/dose)	Early sequestration on ECMO circuit which may result in difficulties achieving therapeutic levels early on. Perform therapeutic drug monitoring early and repeat regularly (every 24-48 hours initially) – seek ID specialist/ pharmacist advice.

Table 6: Important drug interactions for azole antifungal agents

Check drug interactions with cancer care therapy. The table below contains some of the common interactions seen, however is not an exhaustive list. Consult treatment/clinical trial protocol before commencing.

Medication	Interaction	Management
Prolonged QT interval		
Arsenic trioxide, Macrolide & quinolone antibiotics, conventional antipsychotics, ondansetron, immunosuppressants (ciclosporin), methadone	Additive risk of QT prolongation in setting of azole prophylaxis	Use combination with 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. **Arsenic trioxide:** consider withholding all azoles the day before, the day of and the day after last arsenic dose. Monitor for toxicity. In event of IFI treatment, use alternative non-azole agent specified in Table 1. **Methadone:** Consider alternatives to this combination. If use is necessary, monitor clinical response to methadone closely. Specifically, monitor for evidence of respiratory depression and QTc interval prolongation and arrhythmias (including torsades de pointes). Methadone dose reductions may be required when used with voriconazole, posaconazole, itraconazole or fluconazole. Patients with other risk factors (eg, bradycardia, hypokalaemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these potentially life-threatening toxicities. For further information on risk categories for Drugs that Prolong QT & induce Torsades de Pointes (TdP) - refer to https://www.crediblemeds.org/new-drug-list/

Table 6: Important drug interactions for azole antifungal agents (continued).

Medication	Interaction	Management
Decreased plasma concentration of azoles		
Rifampicin, rifabutin	Induces azole metabolism.	Avoid combination where possible. An increase in azole dose and more frequent TDM may be required.
Carbamazepine, Phenobarbitone	Induces azole metabolism (fluconazole, itraconazole, voriconazole, posaconazole)	
Phenytoin	Induces azole metabolism (fluconazole, 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	Posaconazole suspension absorption reduced due to changes in gastric pH, decreasing Posaconazole levels.	Perform Posaconazole TDM, in particular when starting or stopping proton pump inhibitors. Note: Omeprazole and Esomeprazole has less of an impact on Posaconazole absorption from Modified release tablets.
Paxlovid ® (Nirmatrelvir/ Ritonavir)	Lower dose ritonavir (100 mg every 12 hours) administered in a similarly designed study was associated with a 39% decrease in the AUC of voriconazole. There is some evidence the magnitude and direction of this interaction may depend on CYP2C19 metaboliser status.	Avoid combination where possible, unless ID specialist guidance suggests the benefit outweighs the risk. Bidirectional interaction anticipated dependant on CYP2C19 metaboliser status. More frequent voriconazole TDM with careful dose adjustment required. Note: After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect of nirmatrelvir/ritonavir is predicted to mostly disappear after 3 days.
Increased plasma concentration of azoles		
Omeprazole and Esomeprazole	Voriconazole metabolism reduced (CyP 2C19), increasing Voriconazole levels.	Perform Voriconazole TDM, in particular when starting or stopping proton pump inhibitors. Monitor for signs of Voriconazole toxicity. Note: Omeprazole and Esomeprazole may be used to "boost" voriconazole levels in patients with low levels despite dose adjustments. Seek Senior clinical pharmacist advice.

Table 6: Important drug interactions for azole antifungal agents (continued).

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 but can be dose dependent.	Concurrent use of itraconazole is strictly contraindicated. For weekly IV vinca alkaloid: non-azole agent is preferred (see Table 1) For monthly IV vinca alkaloid: consider withholding voriconazole or posaconazole the day before, the day of and the day after vinca alkaloid dose. Monitor for toxicity. In event of IFI treatment, use alternative non-azole agent specified in Table 1. Fluconazole (at max 6 mg/kg) can be used in most instances. If patient is on fluconazole 12mg/kg (treatment dose), consider withholding fluconazole the day before, the day of and the day after vinca alkaloid dose. Monitor for toxicity. In event of IFI treatment, use alternative non-azole agent specified in Table 1.
Tyrosine kinase inhibitors (TKI), JAK 1/2, ALK, EGFR, VEGFR, Proteosome inhibitors (eg. imatinib, ruxolitinib, sorafenib, dasatinib, nilotinib, crizotinib, erlotinib, pazopanib, sunitinib, ceritinib) **Venetoclax**	TKI metabolism reduced (CyP 3A4 inhibition and/or P-glycoprotein/ABCB1 Inhibitors), 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 (see Table 1) Baricitinib, used as part of acute COVID-19 management, does not appear to interact with itraconazole, voriconazole, Posaconazole and fluconazole.
Bortezomib and Carfilzomib	Bortezomib (or Carfilzomib) 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 (see Table 1).
Warfarin	A Two-fold increase in prothrombin times have been observed in patients receiving Warfarin, who were commenced on Voriconazole.	Monitor for increased anticoagulant effects (e.g., INR, bleeding) if voriconazole is initiated/dose increased, and decreased effects if voriconazole is discontinued/dose decreased. Itraconazole, ketoconazole, or posaconazole may affect the anticoagulant less than voriconazole.
Paclitaxel and Docetaxel	Azoles are likely to interfere with CYP3A4-mediated docetaxel and paclitaxel metabolism, increasing the risk for taxane toxicity.	Avoid concomitant use of strong CYP3A4 inhibitors such as itraconazole, voriconazole and Posaconazole. Monitor for taxane toxicity if using fluconazole (max 6mg/kg/day).

Table 6: Important drug interactions for azole antifungal agents (CONTINUED)

Medication	Interaction	Management
Increased plasma concentration of co-administered drug		
Sirolimus, Tacrolimus, Ciclosporin, Everolimus, Temsirolimus	Metabolism reduced (CyP 3A4 inhibition), 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, ciclosporin or everolimus levels. Dose reduction is often required- seek Senior pharmacist advice. Consider Ciclosporin, Tacrolimus and sirolimus dose reduction of 25-30% in patients commencing on voriconazole, posaconazole or fluconazole (treatment dose 12 mg/kg). Itraconazole should be used with extreme caution in patients on sirolimus.
Busulfan, High dose Cyclophosphamide, Etoposide, Ifosfamide, High dose Methotrexate and Thiotepa	P-glycoprotein/ ABCB1 Inhibitors and CyP3A4 inhibitors may increase the serum concentration of P-glycoprotein/ABCB1 Substrates and CyP 3A4 substrates.	Monitor levels (methotrexate, busulfan) and manage toxicity in consultation with Oncologist. During HSCT conditioning, withhold voriconazole, itraconazole or posaconazole (but not fluconazole) for 7 days prior to starting Busulfan, Thiotepa or High dose cyclophosphamide . Monitor for toxicity. Use alternative non-azole agent specified in Table 1. Consider withholding voriconazole, itraconazole or posaconazole the day before, the day of and the day after ifosfamide, etoposide and high dose methotrexate (until methotrexate level <0.1micromol/L) doses. Monitor for toxicity. In event of IFI treatment, use alternative non-azole agent specified in Table 1. Fluconazole (at max 6mg/kg) can be used in most instances. If patient is on fluconazole 12 mg/kg (treatment dose), consider withholding fluconazole the day before, the day of and the day after ifosfamide doses. In event of IFI treatment, use alternative non-azole agent specified in Table 1.
Diazepam, midazolam	Benzodiazepine metabolism reduced, increasing risk of toxicity including respiratory depression	Monitor for signs of benzodiazepine toxicity
ATRA (all trans retinoic acid)	ATRA metabolism reduced (CyP 3A4 inhibition) increasing risk of toxicity and ATRA Differentiation syndrome	Concurrent use of itraconazole, fluconazole, voriconazole and posaconazole is *not recommended* in most protocols. A non-azole agent is mandated for all patients receiving ATRA (see Table 1)
Paxlovid ® (Nirmatrelvir/ Ritonavir)	Posaconazole is a strong inhibitor of CYP3A4 and could potentially increase nirmatrelvir/ritonavir exposure, although to a limited extent. Coadministration of nirmatrelvir/ritonavir with itraconazole (a strong CYP3A4 inhibitor) increased nirmatrelvir AUC and Cmax by 39% and 19%.	Use combination with caution and monitor for nirmatrelvir side effects. Note: After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect of nirmatrelvir/ritonavir is predicted to mostly disappear after 3 days.

Medication	Interaction	Management
Increased plasma concentration of co-administered drug		
Sildenafil **Bosentan** **Macitentan**	Itraconazole, Posaconazole and Voriconazole are strong inhibitors of CYP3A4 and is likely to increase sildenafil exposure (2.5 fold increase in Sildenafil AUC) Fluconazole is a moderate inhibitor of CYP3A4 and is less likely to significantly increase sildenafil exposure (especially at 6mg/kg/day dosing).	Posaconazole, Voriconazole and Itraconazole: Avoid combination with sildenafil, bosentan or macitentan where possible. Close monitoring for sildenafil/bosentan/macitentan toxicity required if used in combination. Fluconazole: Can be used concurrently with sildenafil at fluconazole doses of 6mg/kg/day. Close monitoring for sildenafil toxicity required if used in combination with fluconazole at 12mg/kg/day. Seek Cardiologist advice on dose adjustment for Sildenafil to minimize side effects/toxicity. Do not cease or withhold sildenafil without specialist advice (indication: pulmonary hypertension). Seek ID and Cardiology specialist advice for patients on bosentan or macitentan – risk versus benefit consideration required. Consider alternative antifungal therapy where clinically appropriate.

Useful drug interaction resources for comprehensive drug interaction information:

- UpToDate ® Drug Interactions (Available via subscription)
- Flockhart Cytochrome P450 Drug Interaction Table, Division of Clinical Pharmacology, Indianna University
- Micromedex ® 2.0 Drug Interactions search. Truven Health Analytics ® (Available via CKN)
- Liverpool COVID 19 therapies interaction checker is very useful: https://www.covid19-druginteractions.org/checker

List of abbreviations and definitions

ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AUC	Area Under the Curve
BMT	Bone marrow transplant
CGD	Chronic Granulomatous Disease
CHQ	Children's Health Queensland
CKN	Clinicians Knowledge Network
CYP450	Cytochrome P450 enzyme system
ECIL	European Conference on Infections in Leukaemia
ECMO	Extracorporeal Membrane Oxygenation
GM	Galactomannan
GvHD	Graft-versus-Host-disease
HCT	Haematopoietic cell transplantation
HSCT	Haematopoietic stem cell transplantation
IA	Invasive aspergillosis
ID	Infectious diseases specialist
IFI	Invasive fungal infection
IV	Intravenous
IMPS	Infection Management and Prevention service (CHQ)
LCH	Langerhans Cell Histiocytosis
PBS	Pharmaceutical Benefit scheme
PID	Primary Immune deficiency
PO	Per oral
SAA	Severe Aplastic Anaemia
SCN	Severe Congenital Neutropenia
SCID	Severe Combined Immunodeficiency Disorder
SCUF	Type of dialysis/ultrafiltration with ECMO
TDM	Therapeutic drug monitoring
WAS	Wiskott-Aldrich Syndrome
VA	Veno-arterial
VV	Veno-venous

References and suggested reading

1. Dvorak CD et al. Antifungal prophylaxis in Pediatric hematology/Oncology: New choices and new data. Pediatr Blood Cancer 2011.
2. Lehrnbecher T, Ethier MC, Zaoutis T, Creutzig U, Gamis A, Reinhardt D, Aplenc R, Sung L. International variations in infection supportive care practices for paediatric patients with acute myeloid leukaemia. Br J Haematol. 2009 Oct;147(1):125-8. doi: 10.1111/j.1365-2141.2009.07844.x. Epub 2009 Aug 5.
3. Neely, M., T. Rushing, A. Kovacs, R. Jelliffe, and J. Hoffman. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis 2010;50:27-36.
4. Quarello, P., Saracco, P., Giacchino, M., Caselli, D., Caviglia, I., Longoni, D., Varotto, S., Rana, I., Amendola, A., Misuraca, A., Licciardello, M., Paolucci, P., Ladogana, S., Rivetti, E., Dufour, C. and Castagnola, E. (2012), Epidemiology of infections in children with acquired aplastic anaemia: a retrospective multicenter study in Italy. European Journal of Haematology, 88: 526–534. doi: 10.1111/j.1600-0609.2012.01770.x
5. Sung L et al. Infections and Association With Different Intensity of Chemotherapy in Children With Acute Myeloid Leukemia. Cancer 2009:1100-1108
6. Taketomo, C.K. (ed). (2017-2018), In Pediatric Dosage handbook International , 24th edn, Lexi-Comp: USA.
7. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young J, Boeckh MA. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 2009; 15: 1143-1238
8. Tragiannidis A et al. Antifungal chemoprophylaxis in children and adolescents with haematological malignancies and following allogeneic haematopoietic stem cell transplant. Drugs 2012: 72(5)685-704. (LAMB alt day)
9. Di Nardo et al Drugs pharmacokinetics during veno-venous extracorporeal membrane oxygenation in paediatrics. J Thorac Dis 2018; 10 (Suppl 5): S642 – S652
10. Spriet I et al. Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. JAC 2009; 63 (4): 767 – 770
11. Bruggemann RJ et al. Therapeutic drug monitoring of voriconazole in a child with invasive aspergillosis requiring extracorporeal membrane oxygenation. Ther Drug Monit. 2008; 30 (6) 643-646
12. Sherwin J et al. Pharmacokinetics and dosing of anti-infective drugs in patients on extracorporeal membrane oxygenation: a review of the current literature. Clin Ther: 2016; 38 (9): 1976 – 1994
13. Cohen-Wolkowiez M et al. Safety and pharmacokinetics of Multiple-dose anidulafungin in infants and neonates. Clin Ther. 2011; 89 (5): 702-707
14. Aguilar G et al. Pharmacokinetics of anidulafungin during venovenous extracorporeal membrane oxygenation. 2016 (20): 325 - 326
15. Autmizguine J et al. Pharmacokinetics and safety of micafungin in infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J 2016; 35(11): 1204-1210
16. Watt KM et al. Fluconazole population pharmacokinetics and dosing for prevention and treatment of invasive candidiasis in children supported with extracorporeal membrane oxygenation. AAC 2015; 59 (7): 3935 – 3943
17. Koch BCP et al. Insufficient serum caspofungin levels in a paediatric patient on ECMO. Medical Mycology Case reports 2013 (2): 23 24
18. Vermes A et al. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. JAC 2000 (46): 171 -179
19. Boonsathorn, S et al. Clin Pharmacokinet Clinical Pharmacokinetics and Dose Recommendations for Posaconazole in Infants and Children (2018). https://doi.org/10.1007/s40262-018-0658-1
20. Cheng V et al. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. J Thorac Dis 2018; 10 (Suppl 5): S629-S641
21. Shekar K et al. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. Journal of Critical care 2012 (27): 741.e9 – 741.e18

22. Ashbee HR et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society of Medical Mycology. JAC 2014; 69: 1162-1176
23. Pea F et al. Overview of antifungal dosing in invasive candidiasis. JAC 2018; 73: Suppl 1: i33-i43
24. Van der Elst et al Insufficient Fluconazole Exposure in Pediatric Cancer Patients and the Need for Therapeutic Drug Monitoring in Critically Ill Children. Clinical Infectious Diseases 2014;59(11):1527–33
25. Fleming S, Yannakou CK, Haeusler GM, Clark J, Grigg A, Heath CH, Bajel A, van Hal SJ, Chen SC, Milliken ST, Morrissey CO, Tam CS, Szer J, Weinkove R, Slavin MA. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014. Intern Med J. 2014 Dec;44(12b):1283-97. doi: 10.1111/imj.12595. PMID: 25482741
26. Groll et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation *Lancet Oncol* 2014; 15: e327–40 (LAMB alt day)
27. Chen SC et al. Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care settting. IMJ 2014(44);1315-1322. ,(paed dosing, candida)
28. The Royal Children's Hospital Clinical Practice Guideline Antifungal prophylaxis for children with cancer or undergoing haematopoietic stem cell transplant**:** https://www.rch.org.au/clinicalguide/guideline_index/Antifungal_prophylaxis_for_children_with_cancer_or_undergoing_haematopoietic_stem_cell_transplant/ and https://www.rch.org.au/uploadedFiles/Main/Content/clinicalguide/guideline_index/Antifungal_prophylaxis_GL_table_2.pdf
29. Muilwijk EW et al. Pharmacokinetics of extended dose intervals of micafungin in haematology patients: optimizing antifungal prophylaxis. J Antimicrob Chemother 2018; 73: 3095–3101
30. Lehrnbecher T et al. Extended Dosing Regimens for Fungal Prophylaxis. Clin Microbiol Rev 2019; 32 (2): e00010-19
31. Wang S et al. Invasive fungal infections in children with acute lymphoblastic leukaemia: Results from four Australian centres, 2003-2013. Pediatr Blood Cancer. 2019;66:e27915.
32. Wasmann RE et al. Fixed Dosing of Liposomal Amphotericin B in Morbidly Obese Individuals. Clinical Infectious Diseases. 2020;70(10):2213–5

Acknowledgement

The Royal Children's Hospital Clinical Practice Guideline Antifungal prophylaxis for children with cancer or undergoing haematopoietic stem cell transplant:

https://www.rch.org.au/clinicalguide/guideline_index/Antifungal_prophylaxis_for_children_with_cancer_or_undergoing_haematopoietic_stem_cell_transplant/

Consultation

Key stakeholders who reviewed this version:

- Paediatric Infectious Diseases Consultant team (IMPS)
- Paediatric Oncology Consultant Team
- Clinical Pharmacist Lead- Oncology
- Senior Clinical Pharmacist – Oncology
- Clinical Pharmacist Lead - Antimicrobial Stewardship
- Medicines advisory committee – Endorsed 21/04/2022

Guideline revision and approval history

Version No.	Modified by	Amendments authorised by	Approved by
1.0 29/11/2013	Paediatric Infectious Diseases Consultant team (IMPS, CHQ) Paediatric Oncology Consultant Team (CHQ) Paediatric Immunologist (CHQ) Clinical Oncology Pharmacy Manager (CHQ) Antimicrobial Stewardship Pharmacist (CHQ)	Medicines Advisory Committee (MAC)	General Operations Manager
2.0 17/01/2020	Director, Infection Management and Prevention Service Pharmacist Lead- Antimicrobial Stewardship (CHQ)	Medicines Advisory Committee (MAC)	Executive Director Clinical Services (QCH)
3.0 09/09/2021	Director, Infection Management and Prevention Service Pharmacist Lead- Antimicrobial Stewardship	Director, Infection Management and Prevention Service	Divisional Director Medicine
4.0 16/03/2022	Director, Infection Management and Prevention Service Pharmacist Lead- Antimicrobial Stewardship	Director, Infection Management and Prevention Service	Divisional Director Medicine
4.1 09/04/2024	Governance Officer (Documents)	Pharmacist Antimicrobial Stewardship	Executive Director Clinical Services

Keywords	Antifungal, Anti-mould, Prophylaxis, Treatment, Oncology, Immunocompromised, fluconazole, posaconazole, voriconazole, itraconazole, micafungin, anidulafungin, caspofungin, amphotericin liposomal, Ambisome®, flucytosine, terbinafine, ECMO, therapeutic drug monitoring, neonate, child, adolescent, drug interaction, Relapsed ALL, AML, SCID, PID, HSCT, LCH, Stage 4 Neuroblastoma, GVHD, Severe aplastic anaemia, Aspergillus, Candida, Fusarium, Mucormycosis, Scedosporium, 01075
Accreditation references	National Safety and Quality Health Service Standards (1-8): 3: Preventing and Controlling Healthcare-Associated Infection, 4: Medication Safety ISO 9001:2015 Quality Management System (4-10)