# Guideline

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

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## HUMAN RIGHTS

This governance document has been human rights compatibility assessed. No limitations were identified indicating reasonable confidence that, when adhered to, there are no implications arising under the *Human Rights Act 2019.*

## 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.

## CONTENTS



# ANTIFUNGAL PROPHYLAXIS AND TREATMENT IN PAEDIATRIC ONCOLOGY PATIENTS AND IMMUNOCOMPROMISED CHILDREN GUIDELINE

## SUMMARY OF PROPHYLAXIS OPTIONS (TABLE 1)

- Fluconazole is appropriate prophylaxis in patients at low risk of mould infections
- 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<br><br>>1 years of age: Voriconazole PO<br><br>Alternative: Posaconazole PO | Posaconazole PO<br><br>Alternative: Voriconazole PO | Micafungin IV – daily (inpatient)<br>Micafungin IV – three times a week (HITH)<br><br>Alternative: Ambisome ®IV |
| | **Infant ALL (< 1 year old at diagnosis)**<br><br>**VHR/ T-cell ALL**<br><br>**HR ALL (induction only)** | Start: when ANC < 1.0 and during intensive phase only (induction, consolidation and delayed intensification)<br><br>Stop: when ANC is ≥1.0 for at least 7 days | | | |
| | **HR ALL** consolidation / delayed intensification | | Fluconazole PO | Fluconazole PO | Micafungin IV – daily (inpatient)<br>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<br><br>Alternative: Posaconazole PO | Posaconazole PO<br><br>Alternative: Voriconazole PO | Micafungin IV – daily (inpatient)<br>Micafungin IV – three times a week (HITH)<br><br>Alternative: Ambisome ®IV |
| | **AML**<br><br>**Infant AML** | Start: following last dose of chemotherapy in cycle or ANC<1.0<br>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<br><br>Alternative: Posaconazole PO | Posaconazole PO<br><br>Alternative: Voriconazole PO | Micafungin IV – daily (inpatient)<br>Micafungin IV – three times a week (HITH)<br>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<br>Stop: day + 100 | Voriconazole PO | Posaconazole PO | |

| 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<br>Stop: when corticosteroid dose is < 0.5mg/kg or 10 mg daily prednisolone equivalent (whichever is less). | Voriconazole PO<br><br>Alternative:<br>Posaconazole PO | Posaconazole PO<br><br>Alternative:<br>Voriconazole PO | Liposomal Amphotericin (Ambisome ®) IV– daily<br>Alternative:<br>Micafungin IV – daily (inpatient)<br>Micafungin IV – three times a week (HITH) |
| **Autologous HSCT** | **Pre-engraftment phase** | Start: during conditioning<br>Stop: when ANC is ≥1.0 for at least 7 days | Fluconazole PO | Fluconazole PO | Micafungin IV – daily<br>Micafungin IV – three times a week (HITH) |
| **Neuroblastoma** | **Stage 4 Neuroblastoma** | Start: with or just after chemotherapy is commenced.<br>Stop: when ANC is ≥1.0 for at least 7 days | Fluconazole PO | Fluconazole PO | Micafungin IV – daily<br>Micafungin IV – three times a week (HITH) |
| **Langerhans Cell Histiocytosis (LCH)** | **LCH Induction therapy** | Start: with or just after chemotherapy is commenced.<br>Stop: when ANC is ≥1.0 for at least 7 days | Fluconazole PO | Fluconazole PO | Micafungin IV – daily<br>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 | | | |

| 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**<br><br>**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<br><br>Alternative:<br>Voriconazole PO<br>Itraconazole PO | Itraconazole PO<br><br>Alternative:<br>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)<br>Alternatives: Voriconazole; Ambisome® IV | Tailor to pathogen once spp and sensitivities |
| **Candida Pyelonephritis / complicated UTI** | Fluconazole IV/oral<br>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<br>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 #<br>Alternatives: Voriconazole, Ambisome® IV. Fluconazole (only if sensitivity confirmed) | |
| **Candida krusei** | First line: Caspofungin IV #<br>Alternatives: Posaconazole, Voriconazole | |
| **Candida parapsilosis** | First line: Fluconazole<br>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<br>Alternative: Ambisome® IV | |
| **Aspergillus terreus** | Voriconazole | Resistant to amphotericin |
| **Lomentaspora / Scedosporium** | First line: Voriconazole and Terbinafine<br>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)<br>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:**<br>3 mg/kg IV three times per week (Mondays, Wednesdays and Fridays of each week)<br>(Max 100 mg/dose)<br>**OR**<br>**1 mg/kg/IV daily (Max 100 mg/dose)**<br>**Neonates:** Limited data. Seek ID specialist advice. | **Infants, children and adolescents:**<br>3 mg/kg to 5 mg/kg IV once daily<br>**CNS disease/meningitis:**<br>5 mg/kg to 7.5 mg/kg IV once daily on advice from ID specialist<br>**Neonates:** Limited data. Seek ID specialist advice. (Conventional amphotericin B (Fungizone®) preferred in neonates)<br>**Obesity:** For patients weighing more than 100 kg, fixed dosing is recommended.<br>3 mg/kg IV daily (Max 300 mg/day) and seek specialist advice<br>5 mg/kg IV daily (Max 500 mg/day) and seek specialist advice. | Not required | Dose based on actual body weight.<br>For patients weighing more than 100 kg, fixed dosing is recommended. See treatment dosing recommendations.<br>Monitor for renal toxicity, electrolyte disturbances (especially hypokalaemia and hypomagnesaemia) and hepatotoxicity.<br>Consider premedication if infusion related adverse effects (inc. fever, chills, rigors) |
| **Anidulafungin** | **Infants, children and adolescents:**<br>1.5 mg/kg IV once daily (Max 100mg/day)<br>**Neonates:** Limited data. Seek ID specialist advice. | **Infants, children and adolescents:**<br>**Loading dose:** 3mg/kg IV as a single dose on day 1 (Maximum 200 mg/day)<br>**Maintenance dose:** 1.5 mg/kg IV once daily from day 2 onwards (Maximum 100 mg/day)<br>**Neonates:** Limited data. Seek ID specialist advice. | Not required | No dose adjustment for renal or liver impairment.<br>Obesity: Increase daily dose by 25-50% of the usual dose in patients weighing >75 kg. |
| **Caspofungin** | **Infants (>3 months), children and adolescents:**<br>50 mg/m2 IV daily (Maximum 50 mg/day)<br>**1 to 3 months of age:** 25 mg/m2 IV daily (Maximum 25 mg/day)<br>**Neonates:** Limited data. Seek ID specialist advice. | **Infants (>3 months), children and adolescents:**<br>**Loading dose:** 70 mg/m2 IV on day 1 (Maximum 70 mg/day)<br>**Maintenance dose:** 50 mg/m2 IV on day 2 onwards (Maximum 50 mg/day)<br>**In critically ill patients**, maintenance dose can be increased to 70 mg/m2/day (maximum 70 mg/day)<br>**1 to 3 months of age:** 25 mg/m2 IV daily (Maximum 25 mg/day)<br>**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.<br>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%.<br>Obesity: Increase daily dose by 25-50% of the usual dose in patients weighing >75 kg. |

| Antifungal | Prophylaxis | Treatment | TDM | Comments |
|---|---|---|---|---|
| **Fluconazole** | **Infants, children and adolescents:**<br>6 mg/kg (maximum 400 mg) oral/IV once daily<br>**Term Neonates:**<br>**Week 1 of life:**<br>3 mg/kg/dose to 6 mg/kg/dose oral/IV twice weekly<br>**Week 2 to 4 of life:**<br>6 mg/kg/dose oral/IV every 72 hourly | **Infants, children and adolescents**:<br>**Loading dose:** 12 mg/kg (maximum 800 mg) IV/oral as a single dose<br>**Maintenance dose:**<br>6 mg/kg (maximum 400 mg) IV/oral once daily<br>Use 12 mg/kg (maximum 800 mg) IV/oral once daily if Immunocompromised or infection is severe<br>**Term Neonates:**<br>**Loading dose:** 25 mg/kg IV as a single dose<br>**Maintenance dose:**<br>**Week 1 of life:** 12 mg/kg IV/oral every 48 hourly<br>**Week 2 to 4 of life:** 12 mg/kg IV/oral once daily | Not routinely required.<br>Advisable for patients with severe IFI, on CRRT or ECMO. Seek ID specialist advice.<br>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.<br>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.<br>Administer with or without food<br>Monitor for rash (rare) and hepatotoxicity (rare)<br>Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs<br>Drug interactions (see Table 5) |
| **Flucytosine** | Seek ID advice. | Administer in combination with susceptible antifungal due to development of resistance. Seek ID advice.<br>**Infants, children and adolescents:**<br>25 mg/kg oral every 6 hourly<br>**Term Neonates:**<br>Week 1 of life: 25 mg/kg oral every 8 hourly<br>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<br>**Treatment:**<br>Trough level: 25 to 50 mg/L<br>Peak level: 50 to 100 mg/L<br>Bone marrow and hepatotoxicity associated with peak levels exceeding 100 mg/L | Dose based on ideal body weight.<br>Monitor FBC, renal and liver function closely (daily initially, then twice a week)<br>Renal impairment – dose adjustment required if CrCl <40 mL/min<br>Hepatic impairment – seek ID specialist advice. |

| Antifungal | Prophylaxis | Treatment | Therapeutic drug monitoring | Comments |
|---|---|---|---|---|
| **Itraconazole** | **Oral solution (Sporanox®):**<br>**1 month to <12 years:** 5 mg/kg oral twice daily (maximum 200 mg/dose)<br>**Neonates:** Limited data. Seek ID specialist advice.<br>**Oral capsules (Sporanox ®): 12 to 18 years:**<br>2.5 mg/kg oral twice daily (maximum 200 mg/dose)<br>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<br>**Prophylaxis:**<br>Trough level<br>≥500 to 1000 microgram/L*<br>**Treatment:**<br>Trough level<br>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)<br>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)<br>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)<br>*Itraconazole levels measured using HPLC method |
| **Micafungin** | **Infants, children and adolescents:**<br>**Inpatient:**<br>1 mg/kg IV daily (Max 100 mg/day)<br>**HITH:**<br>3 mg/kg IV three times a week (Max 200 mg/dose)<br>**Neonates:** Limited data. Seek ID specialist advice. | **Infants and children up to 2 years:**<br>5 mg/kg IV once daily (Max 100 mg/day)<br>**2 to 16 years (up to 40kg):**<br>3 mg/kg IV once daily (Max 100 mg/day*)<br>**16 to 18 years (more than 40kg):**<br>3mg/kg IV once daily (Max 150 mg/day)<br>(* Increase to maximum 200 mg once daily if response is inadequate)<br>**Term Neonates:**<br>General: 4 mg/kg IV once daily<br>CNS infection: 10 mg/kg IV once daily | Not required | May cause histamine induced reaction (rash, facial swelling, pruritus and/or bronchospasm)<br>Obesity: Increase daily dose by 25-50% of the usual dose in patients weighing >75kg.<br>No dose adjustment for renal or hepatic impairment. |
| **Posaconazole** | **See table 4.** | | | |

| Antifungal | Prophylaxis | Treatment | TDM | Comments |
|---|---|---|---|---|
| **Voriconazole** | Optimal dosing for prophylaxis is not established. Australian guidelines recommend using the same doses as for treatment.<br><br>**<u>Infants and children up to 2 years:</u>**<br>9 mg/kg oral twice daily<br><br>**<u>2 to 12 years (up to 50 kg):</u>**<br><br>**Loading dose:** 9 mg/kg oral twice daily for 2 doses (maximum 350 mg/dose)<br><br>**Maintenance dose:** 8 mg/kg oral twice daily (maximum 200 mg/dose)<br><br>**<u>12 to 15 years (less than 50 kg):</u>**<br>**Use dose for children 2 to 12 years (above)**<br><br>**<u>12 to 15 years (more than 50 kg):</u>**<br>**Use dose for adolescents 15 to 18 years (below)**<br><br>**<u>15 to 18 years (more than 50 kg):</u>**<br><br>**Loading dose:** 6 mg/kg oral twice daily for 2 doses (maximum 400 mg/dose)<br><br>**Maintenance dose:** 4 mg/kg oral twice daily (maximum 200 mg/dose)<br><br>**Neonates:** Limited data. Seek ID specialist advice. | **<u>Infants and children up to 2 years:</u>**<br>9 mg/kg IV/oral twice daily<br><br>**<u>2 to 12 years (up to 50 kg):</u>**<br>**Loading dose:** 9 mg/kg IV/oral twice daily for 2 doses<br><br>**Maintenance dose- Intravenous:**<br>8 mg/kg IV twice daily and titrate according to TDM results.<br><br>**Maintenance dose - Oral:** 9 mg/kg oral twice daily (maximum initial dose of 350 mg/dose then titrate according to TDM results)<br><br>**<u>12 to 15 years (less than 50 kg):</u>**<br>**Use dose for children 2 to 12 years (above)**<br><br>**<u>12 to 15 years (more than 50 kg):</u> Use dose for adolescents 15 to 18 years (below)**<br><br>**<u>15 to 18 years (more than 50 kg):</u>**<br><br>**Loading dose:** 6 mg/kg IV/oral twice daily for 2 doses<br><br>**Maintenance dose- Intravenous:**<br>4 mg/kg IV twice daily and titrate according to TDM results.<br>**Maintenance dose- Oral:**<br>4 mg/kg oral twice daily (maximum initial dose of 200 mg/dose then titrate according to TDM results).<br><br>**Neonates:** Limited data. Seek ID specialist advice. | **Prophylaxis:**<br>*Timing:* Trough level on day 5<br><br>*Target:* Trough level 1 to 2 mg/L<br><br>**Treatment:**<br><br>*Timing:* Take trough level (30 minutes pre-dose) before 4th dose as a safety check.<br><br>If level > 4 mg/L, contact ID/ Oncology consultant to discuss dose adjustment.<br><br>Repeat trough level on day 5 (steady state) after starting drug or changing dose.<br><br>*Target:* Trough level 1 to 5 mg/L<br><br>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)<br><br>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).<br>Council on avoidance sun exposure. Reports of skin cancer with prolonged (more than 6 months) use.<br><br>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.<br><br>Obesity: Dose based on adjusted body weight.<br><br>Caution in renal impairment as solubilizer (SBECD) may accumulate. Significance is not known, consult pharmacy.<br><br>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.<br><br>Drug interactions (see Table 5) |

| Antifungal | Prophylaxis | Treatment | TDM | Comments |
|---|---|---|---|---|
| **Terbinafine** | Not routinely used for prophylaxis | **Infants, children and adolescents:**<br>**Weight banded dosing:**<br>10 to 20 kg: 62.5 mg orally once daily<br>20 to 40 kg: 125 mg orally once daily<br>More than 40 kg: 250 mg once daily<br>**Life threatening infection (for example Scedosporium/ Lomentaspora, high dose terbinafine used in combination with voriconazole):**<br>**Seek ID advice.**<br>10 to 20 kg: 125 mg orally once daily<br>20 to 40 kg: 250 mg orally once daily<br>More than 40 kg: 500 mg once daily<br>(Dolton M et al. AAC. 2014; 58 (1): 48-54)<br>**Neonates:** Limited data. Seek ID specialist advice. | Not currently available in Australia. | Take doses with or without food.<br>Monitor for rash, hepatotoxicity and bone marrow toxicity.<br>Disturbances of taste/smell may occur; resolution may be delayed (>1 year) following discontinuation of terbinafine, or in rare cases may be permanent.<br>Renal impairment – dose adjustment required if CrCl less than 50 mL/min.<br>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:**<br>**Therapeutic drug monitoring:** Trough level (30 minutes pre-dose) on day 5 to 7 after starting drug or changing dose<br>**Prophylaxis**: trough ≥ 0.5 to 0.7 mg/L<br>**Treatment:** trough 1 to 3 mg/L<br>Avoid antacids, H2 receptor antagonists, proton pump inhibitors.<br>Monitor for rash (rare), hepatotoxicity (rare), neurotoxicity and GI upset. Monitor for QT prolongation if other risk factors or pro-arrhythmic drugs.<br>No dosage adjustment in renal impairment. Intravenous vehicle may accumulate. Severe hepatic impairment: Seek ID advice. Avoid unless risk/benefit has been assessed.<br>**Additional notes - IV Posaconazole:** Not licensed in children <18 years of age.<br>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:**<br>**Day 1:**<br>300 mg orally twice daily for 2 doses<br>**Maintenance dose:**<br>**Day 2 onwards:**<br>300 mg orally once daily | Seek ID advice | |
| **Posaconazole Intravenous solution** | | | | | |
| **1 to 18 years** | Seek ID advice | Seek ID advice | **Loading dose:**<br>**Day 1:** 10 mg/kg IV twice daily for<br>2 doses (Max 300 mg/dose)<br>**Maintenance dose:**<br>**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<br>Confirm adherence<br>Exclude poor absorption (absorption reduced with severe mucositis and diarrhoea). Depending on agent, diet may also affect absorption (see Table 3)<br>Investigate potential drug-drug interactions (see below and discuss with pharmacy) | Confirm a true trough sample was taken<br>Investigate potential drug-drug interactions (see Table 5 and discuss with pharmacy)<br>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:**<br>**Loading dose:** 3 mg/kg IV as a single dose on day 1 (Maximum 200 mg/day)<br>**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.<br>Use standard dosing (Table 2) and seek ID specialist advice<br>No TDM available |
| **Liposomal Amphotericin B (Ambisome)** | Unchanged | Unchanged | **Infants, children and adolescents:** 3 mg/kg to 5 mg/kg IV once daily<br>**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<br>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:**<br>**Loading dose:** 12 mg/kg IV as a single dose,<br>**Maintenance dose:** 6 mg/kg IV once daily (Max 400 mg/day)<br>**Treatment:**<br>**Loading dose:** 35 mg/kg IV as a single dose,<br>**Maintenance dose:** 12 mg/kg IV once daily (Max 800 mg/day) | Studies reviewed PKPD in infants on ECMO. Higher loading dose recommended.<br>Perform therapeutic drug monitoring – seek ID specialist and Senior pharmacist advice.<br>a Higher AUC target of 800 mg × h/L in immunocompromised and critically ill patients with invasive Candida may be preferred. |

| 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)<br>**2 to 16 years (up to 40 kg):** 3 mg/kg IV once daily (Maximum 100 mg/day)<br>**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<br>Drug is minimally sequestered in ECMO circuit (Sanchez et al, ECCMID 2016)<br>No TDM available |
| **Posaconazole** | Increased | Increased | **Intravenous:**<br>**Loading dose:** 10 mg/kg IV twice daily for 2 doses (Maximum 300 mg/dose)<br>**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)<br>**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.<br>Azoles should not be used in patients with additional cardiac risk factors including reduced left ventricular fraction and electrolyte disturbances.<br><br>**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.<br><br>**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.<br><br>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/ |

| 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.<br><br>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.<br><br>More frequent voriconazole TDM with careful dose adjustment required.<br><br>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.<br><br>Note: Omeprazole and Esomeprazole may be used to "boost" voriconazole levels in patients with low levels despite dose adjustments. Seek Senior clinical pharmacist advice. |

| 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.<br><br>Electrolyte abnormalities, hyponatraemia associated with SIADH and GI upset have also been reported.<br><br>Fluconazole is a weaker CYP3A4 inhibitor so toxicity is rare but can be dose dependent. | Concurrent use of itraconazole is strictly contraindicated.<br><br>For weekly IV vinca alkaloid: non-azole agent is preferred (see Table 1)<br><br>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.<br><br>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)**<br><br>**Venetoclax** | TKI metabolism reduced (CyP 3A4 inhibition and/or P-glycoprotein/ABCB1 Inhibitors), increasing risk of toxicity including QT prolongation and cardiac arrhythmias.<br><br>Refer to chemotherapy protocols for detailed management. | Concurrent use of itraconazole, voriconazole and posaconazole is *not recommended* in most protocols.<br><br>Fluconazole can be used in most instances *except* in combination with sorafenib.<br><br>A non-azole agent is mandated for all patients receiving sorafenib (see Table 1)<br><br>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.<br><br>Monitor for taxane toxicity if using fluconazole (max 6mg/kg/day). |

| 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.<br><br>Reports of significantly increased trough concentrations despite dose reduction, due to combination of itraconazole and sirolimus. | Monitor sirolimus, tacrolimus, ciclosporin or everolimus levels.<br><br>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).<br><br>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.<br><br>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.<br><br>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.<br><br>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.<br>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.<br><br>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**<br>**Bosentan**<br>**Macitentan** | Itraconazole, Posaconazole and Voriconazole are strong inhibitors of CYP3A4 and is likely to increase sildenafil exposure (2.5 fold increase in Sildenafil AUC)<br>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.<br>Fluconazole:<br>Can be used concurrently with sildenafil at fluconazole doses of 6mg/kg/day.<br>Close monitoring for sildenafil toxicity required if used in combination with fluconazole at 12mg/kg/day.<br>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).<br>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

## SUPPORTING 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

## CONSULTATION

Key stakeholders who reviewed this version:

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

## DEFINITIONS

| Term | Definition |
|---|---|
| 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 |

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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/

## GUIDELINE REVISION AND APPROVAL HISTORY

| Version No. | Modified by | Amendments authorised by | Approved by | Comments |
|---|---|---|---|---|
| 1.0 29/11/2013 | Paediatric Infectious Diseases Consultant team (IMPS, CHQ)<br>Paediatric Oncology Consultant Team (CHQ)<br>Paediatric Immunologist (CHQ)<br>Clinical Oncology Pharmacy Manager (CHQ)<br>Antimicrobial Stewardship Pharmacist (CHQ) | Medicines Advisory Committee (MAC) | General Operations Manager | |

| | | | | |
|---|---|---|---|---|
| 2.0<br>17/01/2020 | Director, Infection Management and Prevention Service<br>Pharmacist Lead- Antimicrobial Stewardship (CHQ) | Medicines Advisory Committee (MAC) | Executive Director Clinical Services (QCH) | |
| 3.0<br>09/09/2021 | Director, Infection Management and Prevention Service<br>Pharmacist Lead- Antimicrobial Stewardship | Director, Infection Management and Prevention Service | Divisional Director Medicine | |
| 4.0<br>16/03/2022 | Director, Infection Management and Prevention Service<br>Pharmacist Lead- Antimicrobial Stewardship | Director, Infection Management and Prevention Service | Divisional Director Medicine | |
| 4.1<br>09/04/2024 | Governance Officer (Documents) | Pharmacist Antimicrobial Stewardship | Executive Director Clinical Services | |
| 4.2<br>17/12/2024 | Governance Officer (Documents) | Pharmacist Antimicrobial Stewardship | | |
| 4.3<br>31/03/2025 | Governance Officer (Documents) | Pharmacist Antimicrobial Stewardship | Executive Director Clinical Services | Review extension |

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|---|---|
| **Key words** | 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):<br>• 3: Preventing and Controlling Healthcare-Associated Infection<br>• 4: Medication Safety<br>ISO 9001:2015 Quality Management System (4-10) |