GUIDELINE

Antifungal Prophylaxis - Paediatric

Scope (Staff):	Clinical Staff – Medical, Nursing, Pharmacy
Scope (Area):	Perth Children's Hospital (PCH)

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this disclaimer

Prophylaxis refers to antifungal therapy in a patient at risk of, but without clinical or microbiological evidence of fungal infection. This is distinct from empiric or targeted therapy in a child with clinical features or suspicion of invasive fungal infection.

Azole antifungals have the potential for significant interactions. Ensure drug interactions are checked for all medications including antineoplastic antibodies, kinase inhibitors and biologics.

CLINICAL SCENARIO and RISK FACTORS		DRUGS/DOSES Standard Protocol
Neonates	Neonates with one or more risk factors for candidiasis including: i) ≤ 32 weeks gestation with central line ii) Total parenteral nutrition (TPN) iii) Endotracheal intubation or continuous positive airway pressure (CPAP) iv) All infants with tracheostomy (until discharge from NICU) v) During antibiotic therapy and for 48 hours post completion of course. vi) Systemic corticosteroids **Note:** term babies on antibiotic therapy for <5 days do not require antifungal prophylaxis	**Oral or nasogastric nystatin liquid** 100,000 units (1 mL) three times a day In babies with multiple risk factors and / or who are unable to tolerate oral / nasogastric nystatin, **CONSIDER** changing to **IV fluconazole** prophylaxis (6 mg/kg/dose twice weekly).

CLINICAL SCENARIO and RISK FACTORS		DRUGS/DOSES Standard Protocol
Paediatric Critical Care (PCC)	Critically unwell patients in PCC on broad spectrum antibiotics for longer than one week with two or more risk factors including: i) Invasive ventilation ii) Recent surgery (especially GI surgery) iii) Presence of peritoneal dialysis catheter iv) Central line(s) v) Total parenteral nutrition (TPN)	**Consider:** **Oral or nasogastric nystatin liquid** 100,000 units (1 mL) four times a day
Renal	Patients with peritoneal dialysis catheters in situ **AND** on systemic antibiotics	**Consider:** **Oral or nasogastric nystatin liquid** 100,000 units (1 mL) four times a day **OR** **Oral fluconazole[b]** 3 to 6 mg/kg/dose (to a maximum of 200 mg) every 48 hours
Primary immunodeficiency	Chronic granulomatous disease	**Oral itraconazole capsules (Lozanoc®)** 2.5 mg/kg/DAY (to a maximum initial dose of 200 mg daily). Therapeutic drug monitoring (TDM) required **OR** **Oral itraconazole solution** 2.5 mg/kg/dose (to a maximum initial dose of 200 mg) 12 hourly with TDM **Note**: itraconazole solution and Lozanoc® capsules are not bioequivalent due to differing absorption.
	Other primary immunodeficiency with an increased risk of invasive fungal infection Including: i) Wiskott Aldrich Syndrome, ii) Severe Combined Immunodeficiency (SCID) iii) severe neutropenia	
Solid organ transplantation	Liver Transplantation	**Oral or nasogastric nystatin liquid** 100,000 units (1 mL) four times a day is recommended for the first six months post transplantation
	Kidney Transplantation	Prophylactic antifungals are not routinely recommended
	Other solid organ transplants	Antifungal prophylaxis is indicated. Discuss with interstate transplantation team or PCH Infectious Diseases (ID) team.

<table>
<tr><th colspan="2" rowspan="2">CLINICAL SCENARIO and RISK FACTORS</th><th>DRUGS/DOSES</th></tr>
<tr><th>Standard Protocol</th></tr>
<tr><td rowspan="4">Haematological malignancies</td><td>Acute Lymphoblastic Leukaemia (ALL)[b]
Relapse</td><td rowspan="3">During induction, consolidation and delayed intensification phases and whilst awaiting count recovery following the above phases, use:
IV micafungin
Birth to < 4 months old: 2 mg/kg/dose once daily
Children ≥ 4 months old: 1 mg/kg/dose (to a maximum of 50 mg) once daily
During interim maintenance I and II, maintenance or blinatumomab blocks, antifungal prophylaxis is not routinely recommended.
Posaconazole may be preferable in some high-risk patients depending on drug interactions, discuss with the ID team</td></tr>
<tr><td>Acute Lymphoblastic Leukaemia (ALL)[b]
Infant ALL</td></tr>
<tr><td>Acute Lymphoblastic Leukaemia (ALL)[b]
High risk ALL
(Including AALL1732 & AALL1731 SR-high)</td></tr>
<tr><td>Acute Lymphoblastic Leukaemia (ALL)[b]
Standard risk ALL</td><td>Antifungal prophylaxis is not routinely recommended.
Oral fluconazole[b] may be considered in some children deemed to be at increased risk of mucocutaneous candidal infection.</td></tr>
<tr><td>Acute Myeloid Leukaemia
or Myelodysplastic syndrome [b]</td><td>Oral posaconazole tablets [a,b]
Children ≥ 7 years and able to swallow tablets:
5 to 7 mg/kg/dose (to a maximum of 300 mg) twice a day on day one, followed by 5 to 7 mg/kg/dose (to a maximum of 300 mg) once daily thereafter, with TDM.
Suggested dose bands:
<table>
<tr><th>Weight</th><th>Dose</th></tr>
<tr><td>≥ 15 kg to < 22 kg</td><td>100 mg</td></tr>
<tr><td>≥ 22 kg to < 31 kg</td><td>150 mg</td></tr>
<tr><td>≥ 31 kg to < 36 kg</td><td>200 mg</td></tr>
<tr><td>≥ 36 kg to < 40 kg</td><td>250 mg</td></tr>
<tr><td>≥ 40 kg</td><td>300 mg</td></tr>
</table>
OR
Oral posaconazole suspension [a,b]
Children ≥ 6 months to 12 years old:
4 to 6 mg/kg/dose (to a maximum of 400 mg) three times a day with TDM
Children ≥ 13 years old: 200 mg three times a day, with TDM.</td></tr>
</table>

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<tr><th>Standard Protocol</th></tr>
<tr><td></td><td></td><td>OR
If intravenous therapy required due to intolerance or inadequate therapeutic levels, use:
IV micafungin
Birth to < 4 months old: 2 mg/kg/dose once daily
Children ≥ 4 months old: 1 mg/kg/dose (to a maximum of 50 mg) once daily</td></tr>
<tr><td rowspan="3">Haematopoietic Stem Cell Transplantation (HSCT)</td><td>Allogeneic
stem cell transplantation[b]
Allogeneic HSCT without risk factors for mould infection</td><td>IV or oral fluconazole[b]
6 mg/kg/dose (to a maximum of 400 mg) once daily from end of conditioning</td></tr>
<tr><td>Allogeneic
stem cell transplantation[b]
Allogeneic HSCT with acute graft versus host disease (grade II-IV) or chronic extensive Graft Versus Host Disease (GVHD)</td><td rowspan="2">Oral posaconazole tablets [a,b]
Children ≥ 7 years and able to swallow tablets:
5 to 7 mg/kg/dose (to a maximum of 300 mg) twice a day on day one, followed by 5 to 7 mg/kg/dose (to a maximum of 300 mg) once daily thereafter, with TDM.
Suggested dose bands:
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Oral posaconazole suspension [a,b]
Children ≥ 6 months to 12 years old:
4 to 6 mg/kg/dose (to a maximum of 400 mg) three times a day with TDM
Children ≥ 13 years old: 200 mg three times a day, with TDM.
OR
If an intravenous agent is required due to intolerance or inadequate therapeutic levels, use:
IV micafungin
Birth to < 4 months old: 2 mg/kg/dose once daily
Children ≥ 4 months old: 1 mg/kg/dose (to a maximum of 50 mg) once daily</td></tr>
<tr><td>Allogeneic
stem cell transplantation[b] at high risk of mould infection including children with:
i) primary immunodeficiency
ii) previous HSCT
iii) expected delayed engraftment or graft failure
iv) prior invasive fungal infection (IFI) relapsed leukaemia</td></tr>
</table>

<table>
<tr><th colspan="2" rowspan="2">CLINICAL SCENARIO and RISK FACTORS</th><th>DRUGS/DOSES</th></tr>
<tr><th>Standard Protocol</th></tr>
<tr><td></td><td>Autologous stem cell transplantation (rescue)

Autologous HSCT in neutropenic phase</td><td>IV or oral fluconazole[b]
6 mg/kg/dose (to a maximum of 400 mg)
once daily</td></tr>
<tr><td rowspan="4">Other Oncology/Haematology patients</td><td>High risk neuroblastoma</td><td rowspan="2">Antifungal prophylaxis is recommended during intensive phases of therapy

IV or oral fluconazole[b]
6 mg/kg/dose (to a maximum of 400 mg)
once daily</td></tr>
<tr><td>Hemophagocytic lymphohistiocytosis (HLH) induction therapy</td></tr>
<tr><td>Severe aplastic anaemic (Absolute Neutrophil Count < 0.5 cells/microlitre)</td><td>Antifungal prophylaxis is recommended for children with severe aplastic anaemia
IV or oral fluconazole[b]
6 mg/kg/dose (to a maximum of 400 mg)
once daily
If neutropenia is prolonged (> 4 weeks) despite immunosuppressive therapy,
consider use of a mould-active azole</td></tr>
<tr><td colspan="2">• Based on a past history of fungal infection and exposure to specific chemotherapeutic and biological agents, specific children may be deemed to be at greater risk of invasive fungal infection (IFI).
• Individual prophylaxis plans may be devised and documented in the notes for these children.
• Discontinuation or modification of these individual plans are only to be made following discussion with the treating physician</td></tr>
</table>

a. Administration of posaconazole suspension should be during or after a high-fat meal or Calogen® to optimise absorption. Refer to posaconazole monograph for recommended doses of Calogen®. Proton pump inhibitors significantly reduce oral bioavailability and should be avoided while taking posaconazole.

Given the uncertain and unpredictable pharmacokinetics, therapeutic drug monitoring is recommended when using posaconazole. The target trough concentration for posaconazole prophylaxis is ≥ 0.7 mg/L.

The liquid and tablet formulations of oral posaconazole are NOT interchangeable. The formulation must be specified on each drug order. When prescribing tablets, round to the nearest 50 mg as per the suggested dose bands. There is limited information available regarding halving posaconazole modified release tablets. Case reports have demonstrated target drug levels can be achieved.

b. Due to the potential for significant drug interactions, specific drug-drug combinations should be avoided. Ensure drug interactions are checked for all medications including antineoplastic antibodies, kinase inhibitors and biologics.

- **Bortezomib, Imatinib, Dasatinib:** avoid all azoles (fluconazole, itraconazole, voriconazole and posaconazole).
- **Vincristine, Cyclophosphamide:** avoid all azoles except fluconazole.
- **Gemtuzumab ozogamicin, Inotuzumab ozogamicin:** consider alternative to triazole antifungals, monitor QTc with electrocardiogram (ECG) if concomitant triazole use unavoidable.
- **Gliteritinib, Sorafenib:** consider alternative to triazole antifungals, monitor closely for toxicity if concomitant triazole use unavoidable, including QTc (ECG).
- **Venetoclax:** Venetoclax dose reduction of 50-75% recommended with concomitant triazole antifungal use. Avoid concomitant use during initial venetoclax dose escalation. Seek advice from Oncology / ChAMP pharmacist
- **Ciclosporin, tacrolimus, sirolimus:** dose reduction of these specific immunosuppressive drugs is required when taking posaconazole. Seek advice from Oncology / ChAMP Pharmacist.

Related CAHS internal policies, procedures and guidelines
Antimicrobial Stewardship Policy
ChAMP Empiric Guidelines and Monographs
KEMH Neonatal Medication Protocols

References and related external legislation, policies, and guidelines

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4. Groll AH et al, Lancet Oncology 2014. 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.

5. Hope WW et al, Clin. Micro. and Infection 2012 – ESCMID Guideline for the diagnosis and management of candida disease 2012: prevention and management of invasive infections in noates and children caused by candida spp.

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7. Fleming S et al, Int Med J 2014. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014.

8. Clinical Pharmacology [Internet]. Elsvier BV. 2021 [cited 26/05/2022]. Available from: http://www.clinicalpharmacology-ip.com.pklibresources.health.wa.gov.au/default.aspx. 9. Paediatric Formulary Committee. BNF for Children: 2022. London: BMJ Group Pharmaceutical

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14. Stevens RW, O'Connell C, Huang A, Epps KL, Ilges D. Therapeutic drug monitoring following crushed administration of delayed-release posaconazole tablets via enteral feeding tubes. Journal of Antimicrobial Chemotherapy. 2022;78(2):553-5.

15. Dieringer TD, Schaenman JM, Davis MR. Enteral feeding tube administration with therapeutic drug monitoring of crushed posaconazole tablets and opened isavuconazonium sulfate capsules. J Antimicrob Chemother. 2022;77(5):1417-23.

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