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.

<table>
<tr><th colspan="2" rowspan="2">CLINICAL SCENARIO</th><th rowspan="2">Risk Factors</th><th>DRUGS/DOSES</th></tr>
<tr><th>Standard Protocol</th></tr>
<tr><td rowspan="2">Neonates</td><td>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</td><td>Oral or nasogastric nystatin liquid
100,000 units (1 mL) three times a day</td></tr>
<tr><td colspan="2">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).</td></tr>
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<tr><th>Standard Protocol</th></tr>
<tr><td colspan="4">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)</td><td>Consider:
Oral or nasogastric nystatin liquid
100,000 units (1 mL) four times a day</td></tr>
<tr><td>Renal</td><td colspan="3">Patients with peritoneal dialysis catheters in situ AND on systemic antibiotics</td><td>Consider:
Oral or nasogastric nystatin liquid
500,000 units (5 mL) four times a day
OR
Oral fluconazole[b]
3 to 6 mg/kg/dose (to a maximum of 200 mg) every 48 hours</td></tr>
<tr><td rowspan="3">Primary immunodeficiency</td><td colspan="2">Chronic granulomatous disease</td><td rowspan="2">Other immunodeficiencies at increased risk of invasive fungal infection include: Wiskott Aldrich Syndrome, Severe Combined ImmunoDeficiency (SCID) and severe neutropenia</td><td rowspan="2">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.</td></tr>
<tr><td>Other primary immunodeficiency with an increased risk of invasive fungal infection</td></tr>
<tr><td colspan="2">Children with HIV infection</td><td>Prophylactic antifungals are not routinely recommended</td></tr>
<tr><td rowspan="3">Solid organ transplantation</td><td colspan="3">Liver Transplantation</td><td>Oral or nasogastric nystatin liquid
100,000units (1mL) four times a day
is recommended for the
first six months post transplantation</td></tr>
<tr><td colspan="3">Kidney Transplantation</td><td>Prophylactic antifungals are not routinely recommended</td></tr>
<tr><td colspan="3">Other solid organ transplants</td><td>Antifungal prophylaxis is indicated.
Discuss with interstate transplantation team, the infectious diseases (ID) or
clinical microbiology service</td></tr>
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<tr><th>Standard Protocol</th></tr>
<tr><td rowspan="4">Haematological malignancies</td><td rowspan="4">Acute Lymphoblastic Leukaemia (ALL)[b]</td><td>Relapse ALL</td><td rowspan="3">During induction, consolidation and delayed intensification phases, use:
IV micafungin
Birth to < 4months old: 2 mg/kg/dose once daily
Children ≥ 4 months old: 1 mg/kg/dose (to a maximum of 50 mg) once daily
If Hospital in the Home (HiTH) is unable to accommodate patients on prophylactic micafungin, an alternative agent should be considered in discussion with ID.
Posaconazole may be preferable in some high-risk patients depending on drug interactions, discuss with the ID team</td></tr>
<tr><td>Infant ALL</td></tr>
<tr><td>High risk ALL (including AALL1732 & AALL1731 SR-high)</td></tr>
<tr><td>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 candidial infection.</td></tr>
<tr><td>Haematological malignancies</td><td>Acute Myeloid Leukaemia
or
Myelodysplastic syndrome [b]</td><td></td><td>Oral posaconazole tablets [a,b]
Children 7 to 12 years old and able to swallow whole 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.
Children ≥13 years old: 300 mg twice daily on day one, followed by 300 mg once daily thereafter with TDM.
OR
Oral posaconazole suspension [a,b]
Children ≥ 8 months to 12 years old:
4 mg/kg/dose (to a maximum of 200 mg) three times a day with TDM
Children ≥ 13 years old: 200 mg three times a day, with TDM.
OR
If intravenous therapy required due to intolerance or inadequate therapeutic levels, use:
IV micafungin
Birth to < 4months 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>
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<tr><th>Standard Protocol</th></tr>
<tr><td rowspan="4">Haematopoietic Stem Cell Transplantation (HSCT)</td><td rowspan="3">Allogeneic stem cell transplantation[b]</td><td>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 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]
(preferred if able to swallow whole tablets)
Children 7 to 12 years old: 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 from the end of conditioning, with TDM.
Children ≥13 years old: 300 mg twice daily on day one, followed by 300 mg once daily thereafter from the end of conditioning, with TDM.
OR
Oral posaconazole suspension [a,b]
(if unable to swallow tablets and / or < 7 years old)
Children ≥ 8 months to 12 years old: 4 mg/kg/dose (to a maximum of 200 mg) three times a day TDM.
Children ≥ 13 years old: 200 mg three times a day from the end of conditioning, with TDM.
OR
If an intravenous agent is required due to intolerance or inadequate therapeutic levels, use:
IV micafungin
Birth to < 4months 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 HSCT 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)
v) relapsed leukaemia</td></tr>
<tr><td>Autologous stem cell transplantation (rescue)</td><td>Autologous HSCT in neutropenic phase</td><td>IV or oral fluconazole[b]
6 mg/kg/dose (to a maximum of 400mg) once daily</td></tr>
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<tr><th>Standard Protocol</th></tr>
<tr><td rowspan="4">Other Oncology/Haematology patients</td><td colspan="2">Stage 4 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 colspan="2">Hemophagocytic lymphohistiocytosis (HLH) induction therapy</td></tr>
<tr><td>Aplastic Anaemia</td><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="4">• 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 100 mg tablet. Tablets must not be broken, cut or crushed.

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, Cyclophophamide:** 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

1. Blyth CC et al, JPCH 2012 Chemoprophylaxis of neonatal fungal infections in very low birthweight infants: efficacy and safety of fluconazole and nystatin.

2. Gallin JI et al. NEJM 2003 – Itraconazole to prevent fungal infections in chronic granulomatous disease.

3. Antachopoulos C et al. Clin Micro and Infection 2010 Invasive fungal infections in congenital immunodeficiencies.

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.

6. van Burik JA et al, Clin Infect Dis 2004. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation.

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 Press; 2022.

10.Up to Date [Internet] Wolters Kluwer. 2022. [cited 26/05/22]

11. Li PK-T, Chow KM, Cho Y, Fan S, Figueiredo AE, Harris T, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. Peritoneal Dialysis International. 2022;42(2):110-53.

This document can be made available in alternative formats on request.

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