GUIDELINE	
Antifungal Prophylaxis - Paediatric	
Scope (Staff):	Medical, Nursing and Pharmacy
Scope (Area):	Perth Children's Hospital (PCH)

Child Safe Organisation Statement of Commitment

The Child and Adolescent Health Service (CAHS) commits to being a child safe organisation by meeting the National Child Safe Principles and National Child Safe Standards. This is a commitment to a strong culture supported by robust policies and procedures to ensure the safety and wellbeing of children at CAHS.

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.

<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="3">Neonates</td><td>Preterm infants</td><td>All neonates < 34 weeks gestation or <1500g</td><td>Oral or nasogastric nystatin liquid
100,000units (1mL)
three time a day</td></tr>
<tr><td>All infants with additional risk factors for invasive candida infections</td><td>Neonates with one or more risk factors for candidiasis including :
i) endotracheal intubation;
ii) total parental nutrition;
iii) prolonged (>7 days) broad spectrum antibiotics[a]
iv) systemic steroids</td><td>Oral or nasogastric nystatin liquid
100,000units (1mL)
three time a day</td></tr>
<tr><td colspan="3">In babies with multiple risk factors and/ or who are unable to tolerate oral/nasogastric nystatin, CONSIDER changing to IV fluconazole prophylaxis (6mg/kg/dose twice weekly).</td></tr>
<tr><td rowspan="3">Primary immunodeficiency</td><td colspan="2">Chronic granulomatous disease</td><td rowspan="2">Oral itraconazole syrup
2.5mg/kg/dose
(to a maximum starting dose of 200mg)
12 hourly with therapeutic drug monitoring[b]</td></tr>
<tr><td>Other primary immunodeficien-cy with an increased risk of invasive fungal infection</td><td>Other immunodeficiencies at increased risk of invasive fungal infection include: Wiskott Aldrich Syndrome, Severe Combined ImmunoDeficiency (SCID) and severe neutropenia</td></tr>
<tr><td colspan="2">Children with HIV infection</td><td>Prophylactic antifungals are not routinely recommended</td></tr>
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<tr><th>Standard Protocol</th></tr>
<tr><td rowspan="3">Solid organ transplantation</td><td colspan="2">Liver Transplantation</td><td>Oral or nasogastric nystatin liquid
100,000units (1mL)
four times a day is recommended for the first three months post transplantation</td></tr>
<tr><td colspan="2">Kidney Transplantation</td><td>Prophylactic antifungals are not routinely recommended</td></tr>
<tr><td colspan="2">Other solid organ transplants</td><td>Antifungal prophylaxis is indicated.
Discuss with interstate transplantation team, the infectious diseases or clinical microbiology service</td></tr>
<tr><td rowspan="3">Haematopoietic Stem Cell Transplantation</td><td rowspan="2">Allogeneic stem cell transplantation</td><td>Allogeneic HSCT without risk factors for mould infection</td><td>IV or oral fluconazole
6mg/kg/dose (to a maximum of 400mg)
once daily from end of conditioning</td></tr>
<tr><td>Allogeneic HSCT with acute graft versus host disease (grade II-IV) or chronic extensive GVHD</td><td rowspan="2">Oral posaconazole liquid [c,d,e,f]
Children ≥ 8 months to 12 years old: 4mg/kg/dose (to a maximum of 200mg) three times a day.
Children ≥ 13 years old: 200mg three times a day from the end of conditioning, with therapeutic drug monitoring (TDM).
OR
Oral posaconazole tablets [d,e,f]
Children 7 to 12 years old and able to swallow whole tablets: 5-7mg/kg/dose (to a maximum of 300mg) twice a day on day one, followed by 5-7mg/kg/dose (to a maximum of 300mg) once daily thereafter.
Children ≥13 years old: 300mg twice daily on day one, followed by 300mg once daily thereafter from the end of conditioning, with therapeutic drug monitoring (TDM)
OR
If an intravenous agent is required due to intolerance or inadequate therapeutic levels, use:
IV micafungin
Birth to <4months old: 2mg/kg/dose once daily
Children ≥ 4 months old: 1mg/kg/dose (to a maximum of 50mg)
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)</td></tr>
<tr><td>Autologous stem cell transplantation (rescue)</td><td>Autologous HSCT in neutropenic phase</td><td>IV or oral fluconazole
6 mg/kg/dose (to a maximum of 400mg)
once daily</td></tr>
</table>

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<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="4">Haematological malignancies</td><td>Acute Myeloid Leukaemia
or
Myelodysplastic syndrome [f]</td><td></td><td>Oral posaconazole liquid [c,d,e,f]
Children ≥ 8 months to 12 years old:
4mg/kg/dose (to a maximum of 200mg) three times a day.
Children ≥ 13 years old: 200mg three times a day , with therapeutic drug monitoring (TDM)
OR
Oral posaconazole tablets [d,e,f]
Children 7 to 12 years old and able to swallow whole tablets: 5-7mg/kg/dose (to a maximum of 300mg) twice a day on day one, followed by 5-7mg/kg/dose (to a maximum of 300mg) once daily thereafter and
Children ≥13 years old: 300mg
twice daily on day one,
followed by 300mg once daily thereafter
with therapeutic drug monitoring (TDM)
OR
If intravenous therapy required due to intolerance or inadequate therapeutic levels, use:
IV micafungin
Birth to <4months old: 2mg/kg/dose once daily
Children ≥ 4 months old: 1mg/kg/dose (to a maximum of 50mg)
once daily</td></tr>
<tr><td rowspan="3">Acute Lymphoblastic Leukaemia [f]</td><td>Relapse Acute Lymphocytic Leukaemia</td><td rowspan="2">During intensive phases, use:
IV micafungin
Birth to <4months old: 2mg/kg/dose once daily
Children ≥ 4 months old: 1mg/kg/dose (to a maximum of 50mg)once daily, followed by
IV or oral fluconazole
6mg/kg/dose (to a maximum of 400mg)
once daily

Posaconazole may be preferable in some high risk patients depending on drug interactions, discuss with the infectious diseases team</td></tr>
<tr><td>Infant ALL</td></tr>
<tr><td>High risk ALL</td><td>Standard risk ALL</td><td>Antifungal prophylaxis is not routinely recommended.
Oral fluconazole 6mg/kg/dose (to a maximum of 400mg) once daily may be considered in some children deemed to be at increased risk of mucocutaneous candidial infection</td></tr>
</table>

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<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="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
6mg/kg/dose (to a maximum of 400mg) once daily</td></tr>
<tr><td colspan="2">HLH induction therapy</td></tr>
<tr><td>Aplastic Anaemia</td><td>Severe aplastic anaemic (ANC < 0.5 cells/microlitre)</td><td>Antifungal prophylaxis is recommended for children with severe aplastic anaemia
IV or oral fluconazole
6mg/kg/dose (to a maximum of 400mg) once daily
If neutropenia is prolonged (> 4 weeks) despite immunosuppressive therapy, consider use of a mould active azole</td></tr>
<tr><td colspan="3">• 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>

ALL: Acute Lymphocytic Leukaemia; HSCT: Haematopoietic stem cell transplantation; GVHD: Graft versus host disease; HLH: Hemophagocytic lymphohistiocytosis,

a. Broad-spectrum antibiotics include 3rd generation cephalosporins, beta-lactam/beta-lactamase inhibitors and carbapenems.

b. Doses given are for itraconazole syrup. If Lozanoc® capsules are deemed to be preferable, contact pharmacy for advice regarding dose adjustment. The target trough concentration for itraconazole prophylaxis is ≥500microgram/L. Refer to the ChAMP monograph for further information.

c. Dosage of posaconazole liquid should be during or after a high-fat meal or calogen to optimise absorption. Proton pump inhibitors significantly reduce oral bioavailability and should be avoided.

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

e. The liquid and tablet formulations of oral posaconazole are NOT interchangeable. The formulation must be specified on each drug order.

f. Due to the potential for significant drug interactions, specific drug-drug combinations should be avoided.

   - **Bortezomib, Imatinib, Dasatinib, Sorafenib:** avoid all azoles (fluconazole, itraconazole, voriconazole and posaconazole).
   - **Gemtuzumab ozogamicin**: avoid all azoles (fluconazole, itraconazole, voriconazole and posaconazole) for 5 days after the final dose of Gemtuzumab ozogamicin

- **Vincristine, Cyclophophamide:** avoid all azoles except fluconazole.

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

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. 2019 [cited 14/011/2019].
9. Paediatric Formulary Committee. BNF for Children: 2019. London: BMJ Group Pharmaceutical Press; 2019.

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