EMPIRIC ANTIFUNGAL TREATMENT: MANAGEMENT OF PAEDIATRIC HAEMATOLOGY, ONCOLOGY AND HAEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- The guideline should be used for empiric antifungal therapy in paediatric haematology, oncology and haematopoietic stem cell transplant patients requiring empiric treatment for suspected, probable or proven invasive fungal infection.
- Patients with localising clinical features indicative of invasive fungal infection should be commenced on empiric antifungal therapy and investigated urgently with infectious disease / microbiology consultation (see Algorithm A).
- Patients without localising clinical features indicative of invasive fungal infection should be managed according to fever and neutropenia guidelines (see Algorithm B).

Approved by:	SCHN Policy, Procedure & Guideline Committee	
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CHANGE SUMMARY

- Due for mandatory review. Changes made to table on page 6 and minor re-wording on other pages.

READ ACKNOWLEDGEMENT

- Medical staff prescribing antifungals to this patient group are to read and acknowledge this document.

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Empiric antifungal treatment of paediatric haematology, oncology and haematopoietic stem cell transplant patients

The guideline should be used for empiric antifungal therapy in paediatric haematology, oncology and haematopoietic stem cell transplant patients requiring empiric treatment for suspected, probable or proven invasive fungal infection. The guideline aims to give clinical guidance for the majority of patients but treatment decisions must be tailored to the individual patient and specific clinic situation. Early investigation is encouraged as is consultation with the microbiology / infectious diseases service. This document is intended for internal use only and based on external guidelines, available literature, and expert opinion. The advice provided is at variance with the registered indications and product information for some drugs.

Assessment of baseline risk

The incidence of invasive fungal infection ranges from less than 1% to over 20% with mortality rates ranging from less than 5% to greater than 50% in patients with proven or probable invasive fungal infection.

Patients at high risk of invasive fungal infection (estimated risk ≥10%) include but are not limited to:

- neutropenic patients with persistent or recurrent fever despite prolonged broad-spectrum antibiotic therapy being treated for:
  - acute myeloid leukemia (AML),
  - high risk acute leukaemia. relapsed acute leukaemia, relapsed lymphoma
  - highly myelosuppressive chemotherapy for other malignancies with expected prolonged neutropenia (PMNL $<0.5x10^9$/l for >10 days),
  - allogeneic HSCT recipients (particularly patients with active Graft versus Host Disease and/or ongoing treatment with immunosuppressive agents)
  - recent or ongoing therapy treatment with high dose corticosteroids (for ≥ 2 weeks)

Patients at low risk of invasive fungal infection (estimated risk ≤5%) include but are not limited to:

- Other patients are considered at lower risk of invasive fungal infection but individual patient, clinical, laboratory and environmental factors will influence the risk of invasive fungal infection: e.g. mucositis, prolonged exposure on azole antifungals for prophylaxis or maintenance, or proximity to construction work.

Empiric antifungal therapy

The algorithms provide guidance on commencing empiric antifungal therapy based on:

(i) persisting fever and neutropenia;
(ii) risk of invasive fungal infection (high versus low);
(iii) presence of localising clinical features that may be indicative of a higher risk of invasive fungal infection;
(iv) prior or ongoing mould active azole treatment; and
(v) absence of alternate identifiable clinical causes of infection.

Patients with localising clinical features indicative of invasive fungal infection should be commenced on empiric antifungal therapy and investigated urgently with infectious disease / microbiology consultation (see Algorithm A for investigation, treatment and dosing guidelines). Liposomal amphotericin should be commenced. Patients on mould active azole therapy with clinical or radiographic features indicative of invasive fungal infection should continue with azole therapy in addition to liposomal amphotericin. Patients on mould active azole therapy should have their last trough level checked and a further drug level taken at presentation to confirm adequate trough levels and have their azole dose adjusted appropriately (*see table below*).

Patients without localising clinical features indicative of invasive fungal infection should be managed according to fever and neutropenia guidelines (see Algorithm B). Patients who are currently receiving mould active azole therapy should continue on azole therapy and have trough drug levels taken at presentation to confirm adequate trough levels and have their azole dose adjusted appropriately (*see table below*). Azole trough drug levels are performed 3 times weekly at St Vincent's Hospital, Darlinghurst. Patients with adequate trough drug levels are less likely to have invasive mould infection. Empiric antifungal therapy should be commenced and appropriate investigations performed for patients in the face of persisting fever and neutropenia (5 days) without another identified cause (see Algorithm B).

On commencing empiric antifungal therapy appropriate imaging and investigation is crucial to guide ongoing antifungal therapy. This includes:

- High resolution computerized tomography (CT) of the lungs and targeted imaging of other clinically suspected areas of infection including the abdomen / pelvis and the sinuses (in children ≥ 2 years) is recommended.
- Radiographic findings of invasive fungal infection in immunocompromised paediatric oncology patients may be nonspecific, in particular for children < 5 years.
- Bronchoalveolar lavage (BAL) should be strongly considered for patients at high risk of invasive fungal infection with a nonspecific CT scan
- If the clinical situation allows, the diagnostic evaluation should include, whenever possible, tissue sampling of suspected fungal lesions (e.g. BAL, trans-bronchial or trans-thoracic biopsy for pulmonary lesions, ENT consultation, biopsy and debridement for sinus infection.)
- A repeat CT scan should be performed after 1 week in patients at high risk of invasive fungal infection with ongoing fever and neutropenia where the initial CT scan was nonspecific and no BAL was performed

- Patients with clinical suspicion of CNS infection should have urgent neuroimaging and ID consultation
- Nodular skin lesions should have urgent biopsy for histopathology and cultures.

Table: Recommended therapeutic drug levels

Antifungal	Target trough level for prophylaxis	Target trough level for treatment
Itraconazole	≥500 ng/mL	≥1000ng/mL
Voriconazole	≥1 mg/L to a maximum of 5 mg/L	2 mg/L
Posaconazole	700 to 1250 ng/mL	1250 to 2000 ng/mL
	Recommendation: Levels below these troughs may be inadequate for prophylaxis so the azole dose should be increased so that troughs are consistently within these levels. If troughs are consistently within these levels, invasive mould infection is unlikely and azole prophylaxis should be continued at current dose.	**Recommendation:** For confirmed or probable invasive mould infection, the azole treatment dose should be increased until they are consistently within the target trough.

Specific treatment recommendations:

CT findings suggestive of pulmonary aspergillosis:

- Urgent BAL for airway-focused or proximal lesions.
- Urgent radiology consult for percutaneous biopsy of peripheral lesions.
- Consult Cardiothoracic surgical consultation if lesion adjacent to large vessels or pericardium.
- For children naive to mould active azole prophylaxis, treat with IV voriconazole, aiming for a target trough of 2 to 5mg/L. Higher troughs may be beneficial in the face of refractory disease but need to be balanced against the increased risk of toxicity
- If disease has developed despite adequate troughs for mould-active azole prophylaxis treat with 3mg/kg liposomal amphotericin.
- If zygomycete infection is confirmed or suspected on microscopy, treat with 5mg/kg liposomal amphotericin.
- Review antifungals after 1 week in view of micro and histopathology results

CT findings suggestive of chronic disseminated ("hepatosplenic") candidiasis:

- review lab results for any *Candida sp* isolates
- If disease has developed despite azole prophylaxis, consult radiology regarding biopsy of affected organs, culture accessible sites (throat, urine, etc) for candida to establish prevalent species
- consult Microbiology regarding appropriate therapy
- Treat with appropriate oral agent for at least 3 months

Fungal sinusitis with bony destruction (possible Zygomycete infection):

- Start liposomal amphotericin 5mg/kg
- organise urgent ENT consult re debridement and biopsy
- Review antifungals when microscopy / culture results available
- change to voriconazole if Aspergillus sp or a dematiaceous (black) mould identified

Candidaemia:

- If azole-naïve and not requiring inotropes start IV Fluconazole 12 mg/kg/dose daily (max 800 mg/day)
- If disease has developed despite azole prophylaxis, or if shocked, start EITHER liposomal amphotericin 3mg/kg **OR** IV Caspofungin (age 3 months - 17 years: single loading dose of 70mg/m^2 followed by 50mg/m^2/day (max 70mg); requires phone approval from infectious diseases).
- Remove central venous line promptly if safe to do so.
- After 48 hours liaise with microbiology / infectious diseases re species identification and best therapy.
- Organise dilated pupil fundoscopy for retinitis.
- Organise echocardiogram.
- Perform repeat blood cultures at least 2nd daily until fungaemia has cleared on two consecutive cultures.

Note: The choice of antifungal therapy may need to be modified to take into account known patient (allergies, renal or hepatic dysfunction, fungal prophylaxis or prior fungal infection) and treatment related (known interactions with medications e.g. vinca alkaloids or cyclosporine and azole antifungals) factors.

Management of prolonged fever and neutropenia

Patients with prolonged and profound ongoing neutropenia face an increasing risk of invasive fungal infection without count recovery and are at risk of breakthrough invasive fungal infection despite prophylaxis or empiric therapy. These patients require careful ongoing clinical assessment and investigation. Patients on mould active azole therapy should have regular therapeutic drug monitoring and dose adjustment to maintain azole trough levels in the therapeutic range (see table above). Breakthrough invasive fungal infection on treatment warrants a change in class of antifungal until new invasive antifungal infection can be disproven or confirmed. Appropriate early investigation and consultation with the microbiology / infectious diseases service is encouraged.

Antifungal prophylaxis and cessation of empiric antifungal therapy

Patients with ongoing neutropenia >10 days should continue on prophylactic antifungal therapy. If previously receiving azole prophylaxis and the azole level is therapeutic then liposomal amphotericin should be ceased. Liposomal amphotericin (1mg/kg) should be continued in patients with subtherapeutic azole levels (see table above) for up to 1 week until a therapeutic azole level is achieved. For high-risk patients (see below) in whom azole prophylaxis cannot be used, empiric antifungal therapy should be ceased following resolution of clinical symptoms and peripheral blood count recovery where there is no clinical, imaging or laboratory evidence of invasive fungal infection. For non-high-risk patients (see below), empiric antifungal therapy should be ceased after 4 days (algorithm B), immediately following a normal CT scan (algorithm A), or 1 week after a nonspecific CT scan (Algorithm A)

Antifungal prophylaxis

Secondary Prophylaxis following invasive fungal infection is recommended, targeted against the previous infecting agent, as long as the patient remains neutropenic or immunosuppressed.

Prophylactic antifungal therapy should be considered for patients at high risk of invasive fungal infection patients, for example:

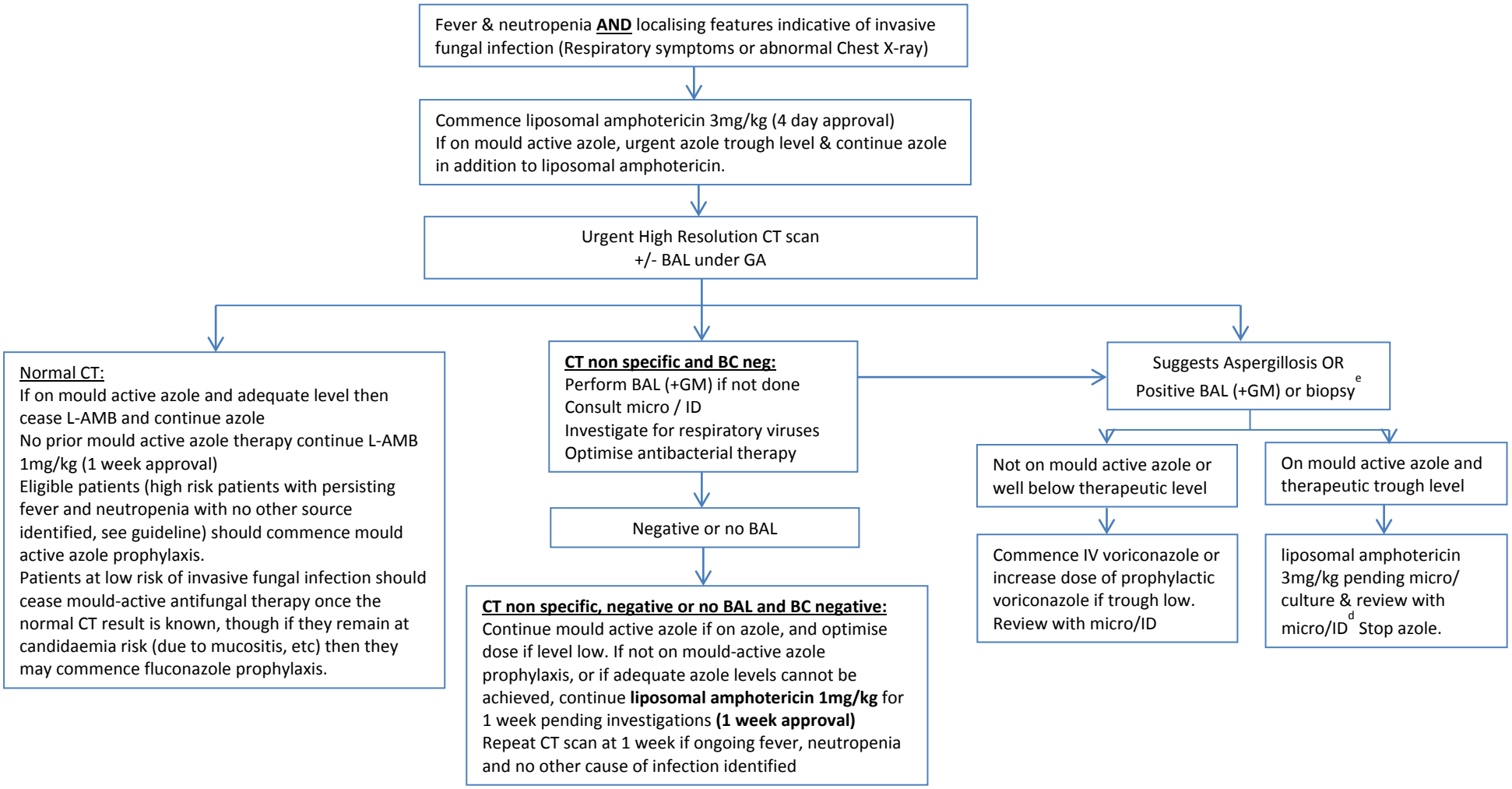
- relapsed or high risk acute leukaemia, relapsed lymphoma (AML, infants)
- highly myelosuppressive chemotherapy for other malignancies with expected prolonged neutropenia (PMNL $<0.5x10^9$/L for >10 days),
- allogeneic HSCT recipients (particularly patients with active Graft versus Host Disease and/or ongoing treatment with immunosuppressive agents)

Fluconazole is PBS approved for prophylaxis of oropharyngeal candidiasis in immunosuppressed patients.

Voriconazole is PBS approved for the treatment and maintenance therapy of definite or probable serious fungal disease in immunocompromised patients but not for prophylaxis.

Posaconazole is not licensed for use in children under 13 years. PBS approved for the (i) treatment of invasive aspergillosis in patients intolerant to, or with disease refractory to, alternative therapy; and (ii) prophylaxis of invasive fungal infections, including both yeasts and moulds, in a patient who is at high risk of developing these infections.

Algorithm A: For patients with localising features indicative of invasive fungal infection



Algorithm B: For patients without localising features indicative of invasive fungal infection