Empirical / pre-emptive antifungal therapy in adult neutropenic patients

Click here for clinical pathway

Definitions

Empirical antifungal therapy: use of antifungals in a neutropenic patient with persisting fever of unknown source despite empirical antibacterial therapy and in the absence of supporting evidence of invasive fungal infection.

Pre-emptive antifungal therapy: use of antifungals in a neutropenic patient with persisting fever despite empirical antibacterial therapy and in the presence of evidence suggestive of invasive fungal infection

Rationale

Recent evidence and guidance supports the use of pre-emptive antifungal therapy in preference to routine use of empirical antifungal therapy in this setting.
Empirical antifungal therapy is generally not advised for patients with an anticipated duration of neutropenia < 10 days.

This flow chart can be used at any time in the management of a neutropenic patient. Typically it will be used in patients with ongoing fever and clinical concern at day 5 review of empirical antibacterial therapy
(See Neutropenic Sepsis - Empirical Antibacterial Therapy Protocol)

Symptoms and signs suggesting possible mucormycosis?
e.g evidence of sinusitis, palatal necrosis, nasal discharge, periorbital oedema/cellulitis, proptosis?

Yes

send cultures if possible

discuss with haematologist / oncologist / microbiologist, ENT surgeon and radiologist

start iv **Ambisome®** 5 mg/kg/day

Review Ambisome® therapy based on investigation results

No

Investigate for evidence of invasive fungal infection:
-clinical assessment including chest (dry cough, dyspnoea, pleuritic pain, pleural rub, haemoptysis are of concern), skin + fundi
-cultures including blood + urine + respiratory secretions (consider BAL), Send serum for **Beta 1-3 glucan** and **aspergillus galactomannan** (and BAL if available for **aspergillus galactomannan)**
- Chest X-ray and high resolution **CT chest upper abdomen** with contrast +/- sinuses.
Note: Whilst **aspergillosis** is often the main concern in this patient group, also consider whether specific additional risk factors for **candidiasis** are present eg patient known to be colonised with candida sp., parenteral nutrition, recent abdominal surgery.

haematologist / oncologist and microbiologist decide to commence or defer antifungal therapy
Note: Typical CT chest abnormality (eg halo sign, air crescent, cavitation) OR Positive aspergillus galactomannan result **OR** fungal hyphae seen or cultured from sputum / BAL. is sufficient evidence to commence pre-emptive antifungal therapy

Defer antifungals

Frequent clinical review

Consider repeat investigations as above; if results suggest fungal infection commence antifungals

Consider antifungal therapy if ongoing clinical concern and risk factors e.g.neutropenia / GVHD

Commence antifungals

1st line – **voriconazole** (Check pre-dose level day 3- 5) iv 6mg/kg every 12 hours for 2 doses then Either: iv 4 mg/kg bd (iv if seriously ill) OR po 200mg bd* (300mg bd* if necessary) *dose reduction if patient <40kg, see BNF

2nd line - **caspofungin** ≥ 80kg; 70mg iv od <80kg; 70mg iv od on Day 1 then 50mg iv od

3rd line - **Ambisome®** iv 3 mg/kg/day

Salvage therapy: discuss apparent treatment failure with microbiologist

Note 1: caspofungin may be the 1st choice in suspected candidiasis
Note 2: previous antifungal prophylaxis and potential drug interactions may affect choice of agent
Note 3: Dosage adjustment / drug alteration for renal or hepatic impairments, please consult ward pharmacist, (e.g. anidulafungin in place of caspofungin in patients with severe hepatic impairment)

Oral switch therapy and treatment duration is assessed on a case by case basis but general principles include:
- Continuation of antifungal therapy until up to 3 days after resolution of profound neutropenia i.e neutrophils >0.5 x 10^9/l.
- Consider oral switch therapy to po voriconazole 200 mg every 12 hours if patient clinically responding and able to tolerate and absorb oral medication.
- Check with pharmacist that drug interactions do not preclude voriconazole therapy.
- Posaconazole may be an alternative oral switch therapy in patients unable to tolerate voriconazole
- Results from large clinical trials of empirical antifungal therapy in neutropenia demonstrate a median treatment duration of approximately 10 days. Duration of pre-emptive antifungal therapy is likely to be longer than this because the probability of invasive fungal infection is greater.