

Clinical Practice Guidelines

FEVER AND SUSPECTED OR CONFIRMED NEUTROPENIA IN CHILDREN

A Collaboration between the Microbiology and
Paediatric Oncology Departments of the
National Cancer Institute Sri Lanka.

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Background

Fever and suspected or confirmed neutropenia is a medical emergency in the paediatric oncology setting.

Antibiotics must be administered **within 30 minutes** if there are signs of sepsis and within 60 minutes if there are no signs of sepsis.

Definitions

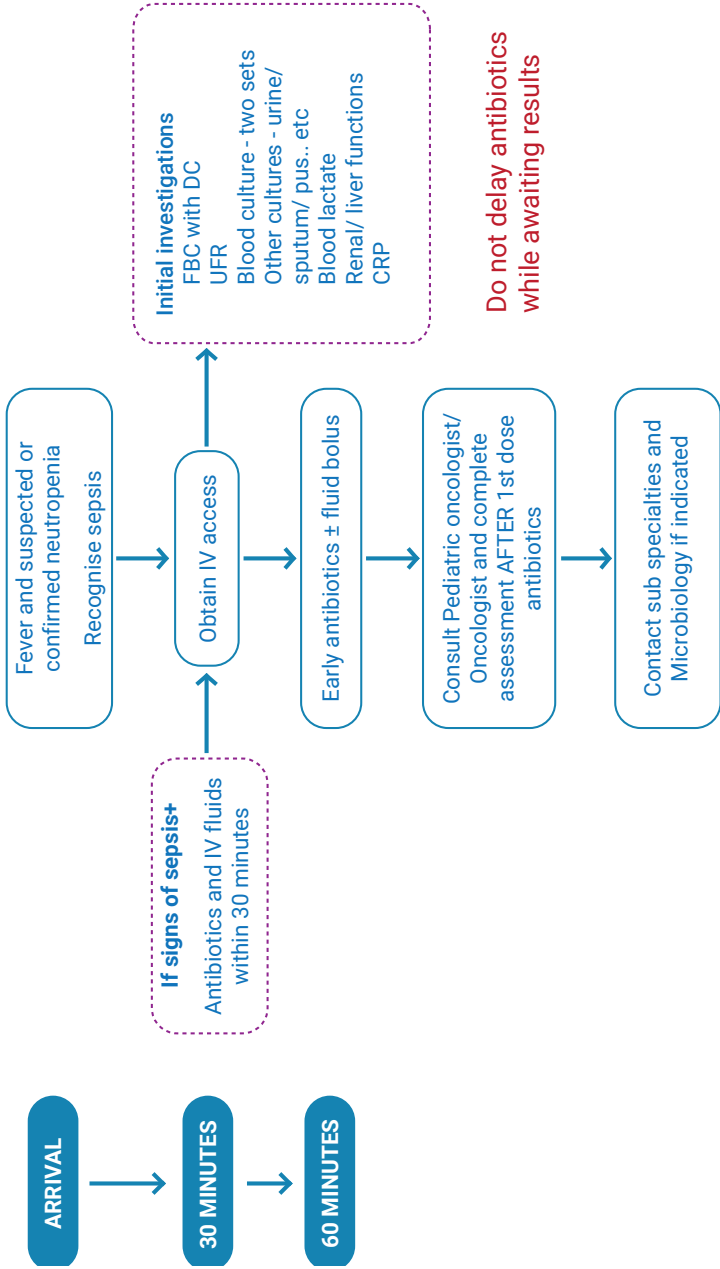
- » **Fever-** A single temperature of $\geq 38.5^{\circ}\text{C}$ or a sustained temperature \geq of 38.0°C over 1 hour.
- » **Neutropenia-** An absolute neutrophil count of $<500/\text{mm}^3$ or $<1000/\text{mm}^3$ with predicted decline to $<500/\text{mm}^3$ over the next 48 hours.
- » **Suspected neutropenia –** Suspect neutropenia in any oncology patient who has received chemotherapy (oral or IV) within the last 14 days.

High risk cancer treatment protocols include but are not limited to

- » Acute myeloid leukaemia (AML) treatment
- » Acute lymphoblastic leukaemia (ALL) induction
- » ALL delayed intensification
- » Infant ALL
- » Lymphoblastic Lymphoma
- » Allogeneic transplant (day 14 to day 365)
- » Autologous transplant (day 7 to day 30)
- » Re-induction chemotherapy for any relapse
- » Chemotherapy which causes severe mucositis

Initial assessment and management

Initial treatment algorithm



Antibiotic recommendations *(No known allergies)*

- » **Initial treatment for all patients-**
 IV Piperacillin tazobactam (if not available consider
 IV Ceftazidime or IV Cefepime)
 +/- IV Amikacin
- » **If severe sepsis or suspected resistant Gram positive infection-** (i.e. cellulitis, obviously infected vascular devices, proven gram positive bacteremia, known MRSA colonization and extensive skin breaks)
 Add IV Vancomycin/ Teicoplanin
- » **In critically ill or haemodynamically unstable** - start
 IV Meropenem/Imipenem + IV Amikacin + IV Vancomycin/
 Teicoplanin
- » **If suspect colitis** - Add Oral or IV Metronidazole

Antibiotic recommendations

(Penicillin/ Beta- lactam hypersensitivity)

- » **Initial treatment for all patients -**
 - Non life threatening hypersensitivity (eg- rash)
 IV Cefepime or IV Ceftazidime
 - Life threatening (immediate) hypersensitivity-
 IV Ciprofloxacin AND IV Vancomycin
 +/- IV Amikacin
- » **If severe sepsis or suspected resistant Gram positive infection** - (i.e. cellulitis, obviously infected vascular devices, proven Gram positive bacteremia, known MRSA colonization and extensive skin breaks)
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Follow up Assessment

After the first dose of antibiotic has been given, complete the following:

A full examination with particular attention to -

- » Upper respiratory tract for otitis media and sinusitis
- » Oropharynx for dental abscess and mucositis
- » Lower respiratory tract for signs of pneumonia, including *Pneumocystis jirovecii* (PJP) pneumonia (cough, tachypnoea, hypoxia, interstitial infiltrate on CXR)
- » Abdomen for signs of *Clostridium difficile* colitis (generalized abdominal pain) or typhilitis (tenderness over caecum)
- » Skin for cellulitis or vesicular lesions
- » Perineum and perianal area for anal fissures, cellulitis or abscess
- » Signs of line/ tunnel/ exit site infection

Additional investigations as indicated-

- » Respiratory symptoms-
 - CXR
 - Nasal swab for respiratory virus PCR
- » Diarrhoea-
 - Stool for culture
 - Stool for *C. difficile* toxin assay if recent treatment with antibiotics
- » CNS symptoms-
 - CT brain and LP
- » Serum procalcitonin levels

Ongoing assessment (Beyond 1st 24 hours)

Clinical assessment- daily

- » Examine for signs of an infective focus
- » Review Microbiology results to guide antibiotic therapy

Repeating blood cultures-

If patient remains febrile, repeat a blood culture set on Day 3

New onset of fever or clinical instability (after being afebrile for > 48 hours)

Modifying antibiotics

- » Based on culture results
- » Based on inflammatory markers- CRP
- » Microbiology opinion

Stopping antibiotics

- » With evidence of marrow recovery- Discontinue empiric antibiotics in patients who have negative blood cultures at 48 hours and who have been afebrile for at least 24 hours
- » Duration of antibiotics also depends on the culture positivity and the site of infection

Prolonged (>72 hours) or recurrent fever despite broad spectrum antibiotics

- » Evaluate and consider treatment for invasive fungal infection (IFI)
- » Evaluate and consider high risk for IFI in patients with conditions below but not limited to,
 - Relapsed acute leukemia
 - AML
 - GVHD
 - Allogenic HSCT
 - Severe aplastic anaemia
 - Prolonged corticosteroid use
 - Prolonged ICU admission

Evaluation for IFI-

- CT –lung and sinuses
- BAL if CT indicates pulmonary infiltrates
- Fungal blood cultures
- BAL and samples from other sterile sites for fungal cultures
- Galactomannan test in serum, BAL

Empirical antifungals-

- Low risk of IFI / mucositis +/- no lung signs
Fluconazole
- High risk of IFI/ lung signs and symptoms present
Amphotericin/ Voriconazole/ Caspofungin

Evidence of bronchopneumonia +

- Oseltamivir
- Erythromycin/ Levofloxacin
- Cotrimoxazole if *Pneumocystis jirovecii* (PJP) pneumonia is suspected

Dose and Frequency

Drug	Dose and frequency
Piperacillin tazobactam	90 mg/kg IV every 6 hourly (1 month to 11 yrs)
Amikacin	7.5 mg/kg IV 12 hourly 15- 22.5mg/day IV divided 8 hourly
Gentamicin	5- 7 mg/kg/day IV once daily or 2.5 mg/ kg 8 hly
Vancomycin	15 mg/kg IV 6 hourly (maximum 500 mg; infusion over 100 minutes) 12- 17 years seriously ill loading dose of 25-30mg/kg
Teicoplanin	10mg/kg IV 12 hourly for 3 doses and then 10mg/kg IV daily
Metronidazole	7.5 mg/kg IV/oral 8 hourly
Cefepime	50 mg/kg (max 2g) IV 12hourly
Ceftazidime	50 mg/kg IV 8 hourly
Ciprofloxacin	10- 15 mg/kg (max 400mg) IV 12 hourly
Meropenem	60 mg/kg/day IV (Divided 8 hly) Meningitis- 120 mg/kg/day IV (divided 8 hourly) Injection on infusion over 15 - 30 minutes
Levofloxacin	16-20 mg/kg/day oral or IV (Divided 12 hourly)
Clarithromycin	15mg/kg/day oral or IV divided 12 hourly Max 1g/day
Co-trimoxazole (Trimethoprim Sulfamethoxazole)	120 mg/kg day oral (2-4 divided doses) for 14-21 days

Drug	Dose and frequency
Fluconazole	If age > 1/12- 6-12 mg/kg/day oral or IV
Voriconazole	Oral- Age 2 - 12 years or 12-14 years and weighing <50 kg- 9/mg/kg (Max 350 mg) bd Age 12- 14 years and weighing >50 kg or age >15 years- Use adult dosing IV- Age 2 to 12 years or 12-14 years and weighing <50 kg- 9/mg/kg IV bd 2 doses then 4-8 mg/kg bd Age 12- 14 years and weighing >50 kg or age >15 years- Use adult dosing
Amphotericin B	After test dose - Conventional- 1 mg/kg/day IV Lyposomal- 3-5 mg/kg/day IV Infusion over 2-3 hours
Anidulafungin	1.5 -3 mg/kg IV loading dose , then 0.75 -1.5mg/kg/day IV Rate of infusion should not exceed 1.1 mg/min
Oseltamivir	Oral - Infant 2 weeks-11 months- 3 mg/kg bd for 5 days <15 kg- 30 mg bd for 5 days >15 kg to 23 kg- 45 mg bd for 5 days >23 kg to 40 kg- 60 mg bd for 5 days > 40 kg- 75 mg bd for 5 days

Following drugs should be given with Consultant Microbiologist opinion.

Drug	Dose and frequency
Colistin	IV Child (body-weight up to 41 kg): 75 000–150 000 units/kg daily in 3 divided doses Child (body-weight 41 kg and above): 9 million units daily in 2–3 divided doses
Tigecycline	IV Child 8–11 years (under expert supervision) 1.2 mg/kg every 12 hours (max. per dose 50 mg) for 5–14 days Child 12–17 years (under expert supervision): 50 mg every 12 hours for 5–14 days
Linezolid	Oral/IV Child 1 month–11 years: 10 mg/kg every 8 hours (max. per dose 600 mg) Child 12–17 years: 600 mg every 12 hours With intravenous use Infusion to be administered over 30–120 minutes.

List of Red light antibiotics

Based on Circular No 01-56/2016 of Ministry of Health- Sri Lanka, following are the antibiotics which need authorization by the Consultant Microbiologist of the hospital prior to prescribing. (Modes of administration- Intravenous, Intramuscular, Oral, Nebulization, Intrathecal, Intraventricular excluding eye and ENT applications).

If required, the clinical team can start the drug urgently informing via telephone by calling or by SMS. Written authorization within 3 days is mandatory.

1. Aztreonam
2. Cefixime
3. Colistin
4. Daptomycin
5. Fusidic acid
6. Linezolid
7. Moxifloxacin
8. Rifampicin
9. Tigecycline
10. Anidulafungin
11. Liposomal amphotericin B
12. Posaconazole
13. Voriconazole
14. Cefoperazone sulbactam

References

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- » National antibiotic guidelines- SLCM 2016
- » BNF for children 2020-2021
- » Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America