Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Febrile Neutropenia

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Febrile Neutropenia

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Definition

Febrile neutropenia (FN) is the occurrence of fever during a neutropenic episode. *Neutropenia* is defined as *absolute neutrophil count (ANC) of <500 cells/mm*^{3}, or an ANC expected to decrease to <500 cells/mm^3 during the next 48 hours.

Definitions Relevant to Febrile Neutropenia

Fever	Fever is defined as a single oral temperature measurement of >38.3°C (101°F) or a temperature of >38.0°C (100.4°F) sustained over a 1-hour period according to the *Infectious Diseases Society of America (IDSA)* Clinical Practice Guideline. Fever is defined as an oral temperature of >38.5°C or two consecutive readings of >38.0°C for 2 hours according to *European Society of Medical Oncology (ESMO)* Clinical Practice Guidelines. The use of rectal temperature which is preferred in some centers should be avoided in children with neutropenic fever.
Neutropenia	Absolute neutrophil count (ANC) <1,000/mm^3.
End of FN episode	Afebrile for >48 hours, recovery of ANC beyond nadir and antibiotic cessation
Severely unwell	Severe sepsis or septic shock (as per Goldstein et al.), altered conscious state (Glasgow Coma Score < 15 or only responsive to voice or pain), documented as "severely unwell" or equivalent in-patient record or either blood pressure or respiratory rate within the mandatory emergency call range.
Bacteremia	A recognized pathogen (including organisms associated with mucosal barrier injury in the setting of mucositis or neutropenia) from ≥1 blood culture set or common commensals from ≥2 blood culture sets drawn on separate occasions.
Microbiologically documented infection	An infection that was clinically detectable and microbiologically proven.
Clinically documented infection	A site of infection that is diagnosed but its microbiological pathogenesis either cannot be proven or is inaccessible to examination.
Likely bacterial infection	Any infection with a microbiologically documented bacterial cause or that was clinically documented in categories typically attributed to bacterial infection, including pneumonia, skin and soft-tissue infection, osteomyelitis or myositis, enterocolitis, otitis media or externa, sinusitis, epididymo-orchitis, central venous catheter pocket or tunnel infection, pharyngitis, perianal abscess or cellulitis, peritonitis, lymphadenitis, or culture-negative sepsis.

Risk Assessment

TABLE 1: Risk assessment of children with febrile neutropenia.

	Low risk	***High risk***
Duration of neutropenia	Below 10 days	Above 10 days
Depth of neutropenia	ANC above 500	ANC below 100
Diagnosis	Solid tumor	Acute leukemia induction chemotherapy, B-NHL
Type of treatment	Conventional chemotherapy	Hematopoietic stem cell transplantation
Disease status	Newly diagnosed other than acute leukemia and B-NHL	Relapsed or refractory malignancy, bone marrow infiltration
Associated features	Nil	☑ Hypotension ☑ Hypoxia ☑ Altered sensorium ☑ Respiratory distress ☑ Mucositis ☑ Abdominal symptoms

(ANC: absolute neutrophil count; B-NHL: B-cell non-Hodgkin lymphoma)

Clinical Features

- ☑ The goal of care is to recognize infection early so that they do not progress from bacteremia to septicemia to septic shock.
- ☑ Neutropenic children do not form an abscess or pus and are unable to localize symptoms.
- ☑ Pain is the only pointer to the source of infection.
- ☑ All mucosal surfaces need to be examined.
- ☑ Check venous access sites thoroughly.
- ☑ Infections arise predominantly from the child's own body bacteria and a thorough history and clinical examination will help guide antibiotic therapy.

Initial Evaluation

- ☑ Complete blood counts
- ☑ C-reactive protein (CRP)
- ☑ Blood culture from peripheral vein
- ☑ Blood culture from all lumens of a central line
- ☑ Baseline blood chemistry (liver and kidney function tests and serum electrolytes)

Other investigations (to be done in case of suggestive symptoms or signs):

- ☑ Urine analysis and urine culture
- ☑ Chest radiograph

Examination (Fig. 1)

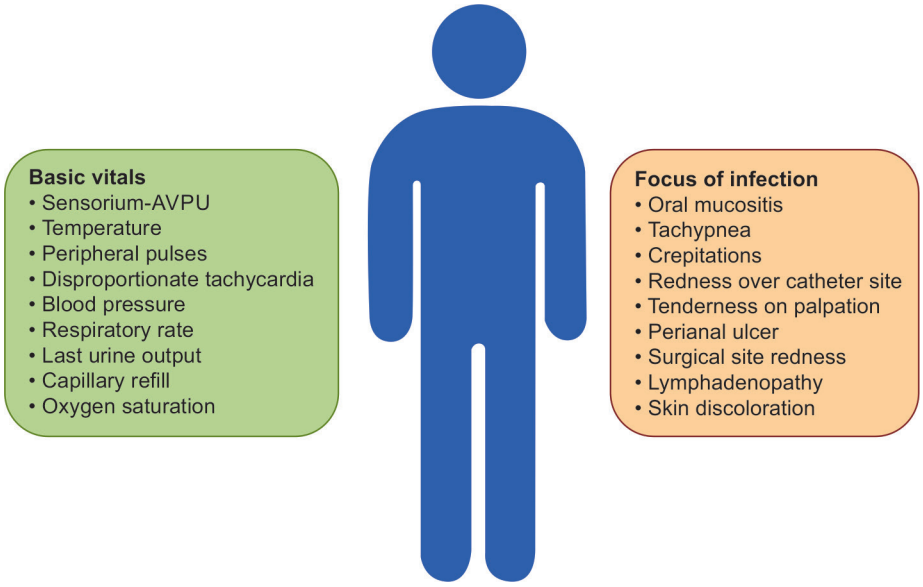


Fig. 1: Examination of a child with febrile neutropenia.
(AVPU: alert verbal painful unresponsive)

Initial Treatment

- ☑ Time to the initial dose of antibiotics should be <60 minutes from the onset of fever *(golden hour)*.
- ☑ The antibiotics should be administered pending the blood counts in a child at risk of FN as delay in antibiotics leads to adverse outcomes.
- ☑ All patients with high-risk FN should be admitted. Patients with low-risk FN may be admitted or managed on out-patient basis.

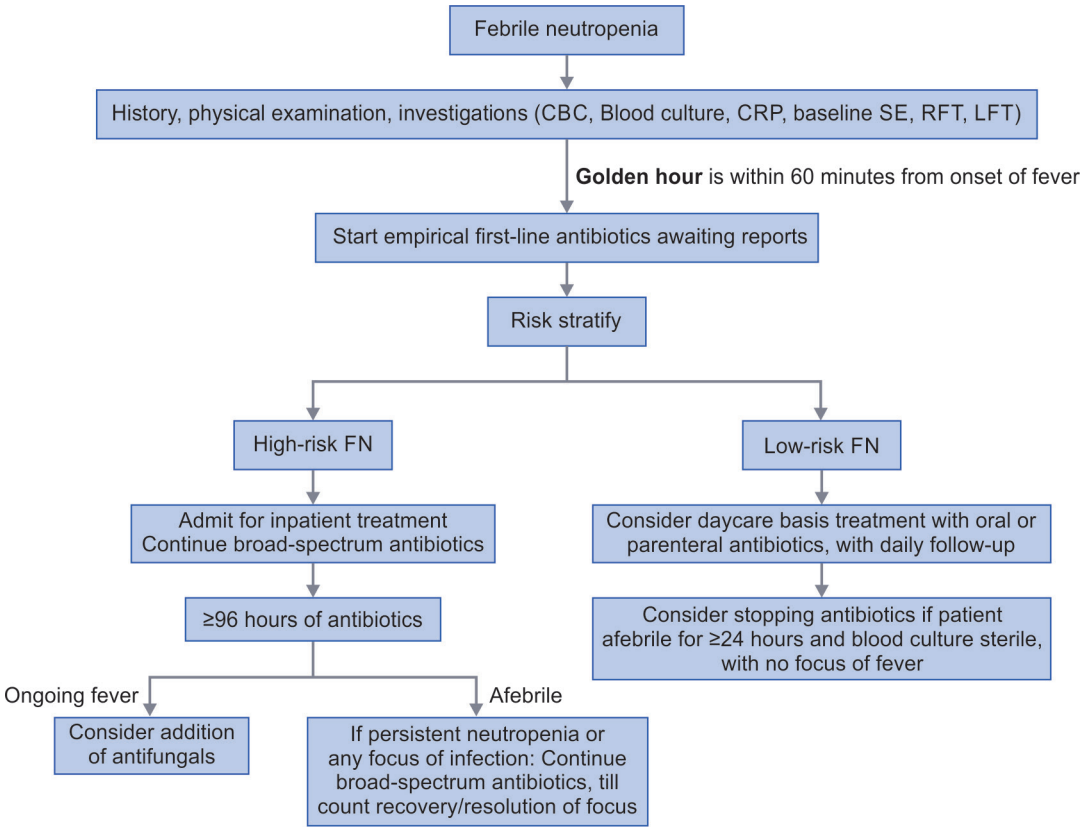
The initial antibiotic cover for a high-risk FN can be:

- ☑ Broad-spectrum beta-lactam antibiotic with antipseudomonal cover like piperacillin-tazobactam at a dose of 100 mg/kg/dose three times a day intravenously.
- ☑ Fourth-generation cephalosporin like cefepime with or without tazobactum at 50 mg/kg per dose two times a day intravenously
- ☑ Carbapenem like meropenem at 40 mg/kg/dose three times a day intravenously
- ☑ Add vancomycin at a dose of 15–20 mg/kg/dose three times a day intravenously in case of clinically unstable patients (hypotension and shock), skin and soft-tissue infection, clinically suspected central line infection, in centers with high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), or hospital-acquired pneumonia.

Management of a low-risk febrile neutropenia:

- ☑ Consider outpatient management with oral antibiotics if patient is accepting well orally. These patients should be monitored closely and followed-up.
- ☑ Parenteral antibiotics may need to be given in a small child, poor oral acceptance or vomiting, or possibility of lack of compliance.
- ☑ Oral antibiotics selection should be done considering local culture sensitivity data, and is typically hospital/center specific.
- ☑ The choice of oral antibiotics can be fluroquinolone like levofloxacin or ciprofloxacin at10–15 mg/kg/day alone, or in combination with amoxicillin-clavulanate at a dose of 50–80 mg/kg/day in two divided doses.

Flowchart 1: Management of febrile neutropenia (FN).



(CBC: complete blood count; CRP: C-reactive protein; LFT: liver function test; RFT: renal function test)

Ongoing Evaluation

In children with ongoing fever, investigations recommended include:

- ☑ Complete blood count (CBC) should be repeated every 2–3 days
- ☑ Blood cultures after 2–3 days; to repeat with any change of antibiotics
- ☑ Inflammatory markers every 2–3 days
- ☑ Liver functions, serum electrolytes, and kidney functions 1–2/week
- ☑ Directed radiological evaluation (chest radiograph, sonography, and chest CT)

Ongoing Management

Uncomplicated FN: Antibiotics may be discontinued in cases where patient has been:

- ☑ Afebrile for 24–48 hours, with evidence of count recovery.
- ☑ Blood culture is sterile.

Change/Upgradation of Antibiotics

- ☑ Fever alone in a stable child with no new focus does not merit a change in antibiotics.
- ☑ Antibiotics should be changed/upgraded in case of:
  - Development of hemodynamic instability
  - Development of a fresh focus of infection
  - Increase in inflammatory markers (CRP and procalcitonin)
  - Blood culture showing growth of a bacteria resistant to first-line antibiotics.

Ongoing Management

Addition of Antifungal Agents

- ☑ Patients at high risk of invasive fungal infection include those with acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), relapsed leukemia, undergoing hematopoietic stem cell transplantation (HSCT), anticipated prolonged neutropenia (≥7 days), and those on high-dose corticosteroids.
- ☑ CT chest should be performed in these patients to look for pulmonary invasive fungal disease (IFD).
- ☑ Serum assay [galactomannan, β-D glucan, and fungal polymerase chain reaction (PCR) assay] are not required in routine.
- ☑ These patients should be started on empirical antifungal therapy in case of FN, with fever persistent beyond 96 hours. The options include:
  - Liposomal amphotericin B (3–5 mg/kg/day)
  - Caspofungin (70 mg/m^2 × 1 day; subsequently 50 mg/m^2/day, once daily)
  - Plain amphotericin B (1–1.5 mg/kg/day) can be used if there is limited access to liposomal amphotericin B or caspofungin
- ☑ Empirical antifungals may be stopped after resolution of fever, provided there is no feature suggestive of IFD.

Supportive Care

- ☑ Transfusion support is required in children with ongoing fever for hemoglobin ≤8 g/dL and platelet count ≤20,000/mm^3
- ☑ Adequate pain relief with opioids should be provided for mucositis, colitis, evolving abscess, or fissures. Morphine (oral or parenteral) at a starting dose of 1 mg/kg/day should be used and titrated as required.
- ☑ Nutritional support, either enteral with nasogastric tube, or parenteral, as required should be ensured.
- ☑ Barrier nursing, hand hygiene, and strict asepsis should be ensured.

Points to Ponder

- ☑ Fever in a neutropenic child is a medical emergency. It requires urgent investigation and usually requires institution of empirical antibiotic therapy.
- ☑ Empirical antibiotic therapy should be initiated as soon as possible (door to needle time <1 hour) after appropriate cultures are taken—*the golden hour.*
- ☑ Do not give paracetamol to a febrile, neutropenic child until it is clear that the criteria for starting antibiotics are fulfilled.
- ☑ Classic signs of infection maybe masked by ongoing treatment, especially steroids during ALL induction and reinduction. If in doubt and a neutropenic child on steroids seems unwell, antibiotics should be initiated after being assessed by the clinician.
- ☑ Observe for the *first 6 hours* before discharge in low risk and always admit high-risk children.
- ☑ Antibiotic policy should be based on local antibiogram data.
- ☑ Antibiotic escalation and de-escalation policy is important in FN patients.
- ☑ Prior stool carbapenem-resistant Enterobacteriaceae (CRE) done or not as in neutropenic patient gram-negative sepsis is most frequent and that is because of invasion of gut bacteria into blood.
- ☑ Prior FN episodes, sensitivity pattern, and institutional standard operating procedure (SOP) to be followed in all FN patients.

Further Reading

- ☑ Bate J, Gibson F, Johnson E, Selwood K, Skinner R, Chisholm J. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients (NICE Clinical Guideline CG151). Arch Dis Child Educ Pract Ed. 2013;98(2):73-5.
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- ☑ Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol. 2017;35(18):2082-94.