

# **MANAGEMENT STRATEGIES FOR FEBRILE NEUTROPENIA**

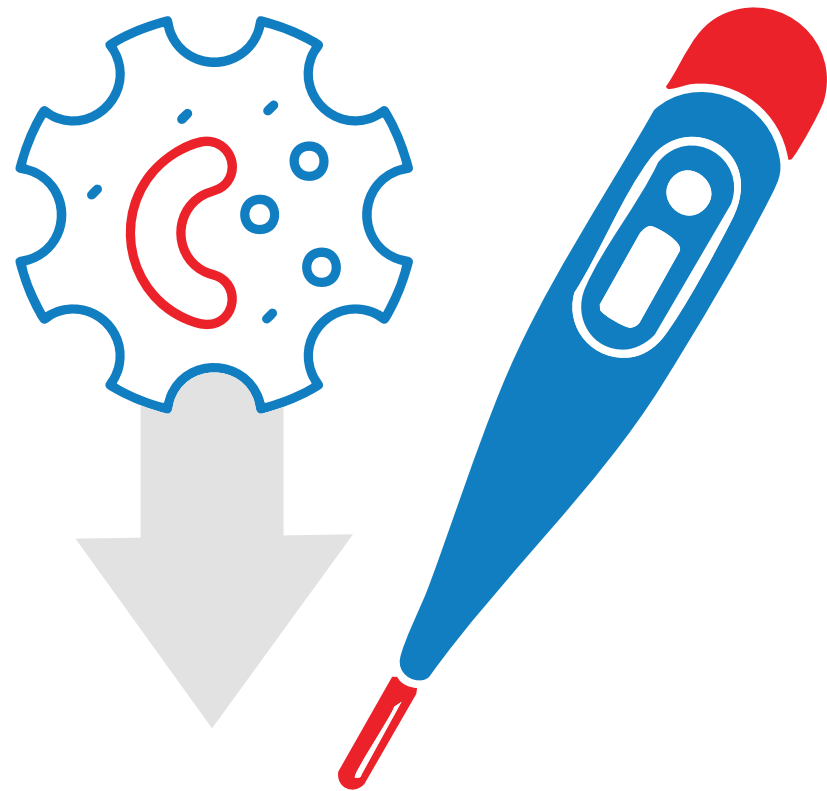
The background features abstract geometric shapes. On the left, there are horizontal bands of blue and red. A large, dark blue chevron shape points towards the right. On the right side, there is a large, light purple trapezoidal shape. A horizontal band with a red-to-blue gradient runs across the top of the image.

SECTION 1:

# **OVERVIEW OF FEBRILE NEUTROPENIA**



# DEFINITION OF FEBRILE NEUTROPENIA



## DEFINITION<sup>1</sup>

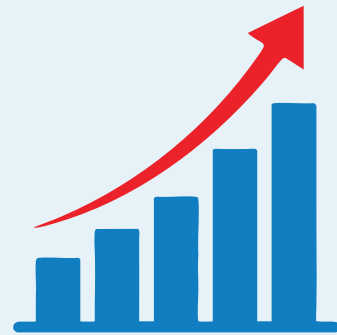
FN is described by clinical practice guidelines as neutropenia with a single oral or tympanic temperature  $\geq 101^{\circ}\text{F}$  ( $38.3^{\circ}\text{C}$ ) or  $\geq 100.4^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ ) for at least one hour.

## SIGNIFICANCE IN PATIENTS WITH CANCER<sup>2,3</sup>

**FN, a common complication of cancer chemotherapy leads to:**

- Delays and dose reductions in chemotherapy
- Compromised efficacy of treatment
- Prolonged hospitalization
- Increased healthcare utilization and costs

# BURDEN OF FEBRILE NEUTROPENIA



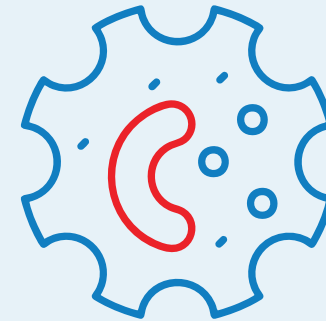
Incidence in Asia:

**10-20%,**

depending on the type of cancer, chemotherapy regimen, and patient risk factors<sup>1</sup>



Indians are at a **higher risk** of developing FN (OR = 1.88), as compared to the Chinese<sup>1</sup>



Indians are more likely to develop **multiple episodes** of FN during treatment<sup>1</sup>



Prevalence of FN in India:

**2-21%<sup>2</sup>**

# EPIDEMIOLOGY OF GRAM-NEGATIVE INFECTIONS ASSOCIATED WITH FEBRILE NEUTROPENIA

## Mumbai, Maharashtra

Prevalence of Gram-negative bacteria in blood cultures: **72%**

Most prevalent organism: *E. coli*<sup>1</sup>

## Bengaluru, Karnataka

Prevalence of Gram-negative bacteria in blood cultures: **58%**

Most prevalent organism: *E. coli*<sup>2</sup>

## New Delhi

Prevalence of Gram-negative bacteria in blood cultures: **93%**

Most prevalent organism: *Klebsiella pneumoniae*<sup>3</sup>

## Kolkata, West Bengal

Prevalence of Gram-negative bacteria in blood cultures: **67.8%**

Most prevalent organism: *Klebsiella oxytoca*<sup>4</sup>



**Gram-negative infections continue to be the predominant cause of FN in Indian patients.<sup>1</sup>**

*E. coli*: *Escherichia coli*; FN: Febrile Neutropenia.

References: 1. Noronha V, et al. Indian J Cancer. 2014;51(4):470-4. 2. K GB, et al. Indian J Surg Oncol. 2024;15(Suppl 2):315-321. 3. Kokkayil P, et al. J Infect Dev Ctries. 2018;12(6):442-447. 4. Mondal PK, et al. J Lab Physicians. 2023;15(1):42-47.

# ETIOPATHOGENESIS OF CANCER-RELATED FEBRILE NEUTROPENIA

## DISEASE-ASSOCIATED FACTORS<sup>1</sup>



Cancer's direct interference with hematopoiesis as in leukemia or metastatic replacement of the bone marrow → Decline in patient's ANC

## TREATMENT-ASSOCIATED FACTORS



Outpatient chemotherapy regimens: The highest reduction in ANC occurs 5-10 days after the last dose<sup>1</sup>

Inpatient chemotherapy regimens (especially for the treatment of hematologic malignancies): Produce a neutropenia of greater depth and duration, both of which amplify the risk<sup>1</sup>

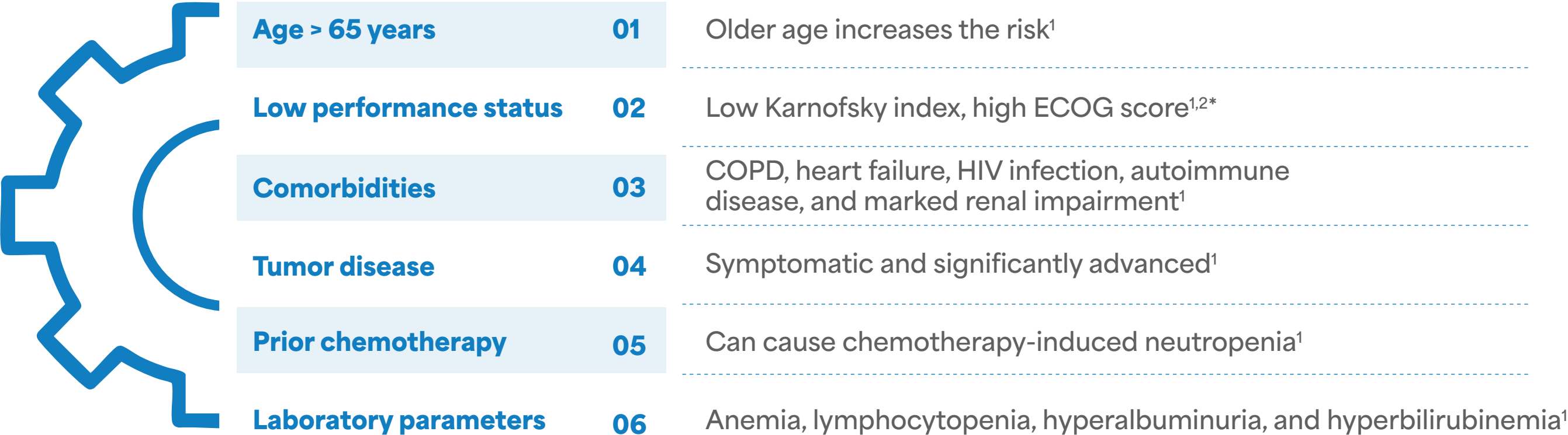
Risk related to the intensity of the chemotherapy regimen:<sup>2</sup>

High-risk FN → Risk > 20%

Intermediate-risk FN → Risk 10-20%

Low-risk FN → Risk < 10%

# FEBRILE NEUTROPENIA: RISK FACTORS AND PREDISPOSING CONDITIONS



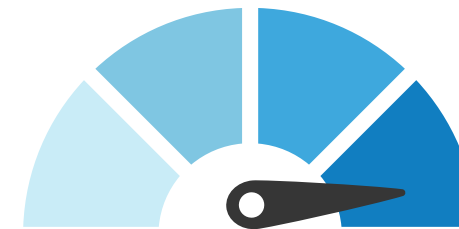
COPD: Chronic Obstructive Pulmonary Disease; ECOG: Eastern Cooperative Oncology Group; HIV: Human Immunodeficiency Virus.  
\*Karnofsky index is the first performance status scale. Using this scale, each patient is allocated a score on a linear scale between 0 (dead) and 100 (normally active), without evidence of disease, summarizing their ability to perform daily activities and the level of assistance they require to do so. An ECOG scale has only six points, ranging from 0 (fully active) to 5 (dead).  
References: 1. Aapro M, et al. Support Care Cancer. 2017;25(11):3295-3304. 2. Kelly CM, et al. J Oncol. 2016;2016:6186543.

# RISK ASSESSMENT OF PATIENTS WITH FEBRILE NEUTROPENIA



## LOW RISK (no high-risk factors and most of the following)

- MASCC risk index score of  $\geq 21$
- Outpatient status at the time of development of fever
- No concomitant acute comorbid illness
- Anticipated short duration of severe neutropenia ( $\leq 100$  cells/ $\mu$ L for fewer than seven days)
- Good performance status (ECOG 0-1)
- No hepatic or renal insufficiency



## HIGH RISK (any factor listed below)

- MASCC risk index score  $< 21$
- Inpatient status at fever onset
- Clinically unstable or significant comorbidities
- Allogeneic HSCT
- Prolonged severe neutropenia (ANC  $\leq 100$  for  $\geq 7$  days)
- Hepatic insufficiency ( $5 \times$  ULN for aminotransferases)
- Renal insufficiency (CrCl  $< 30$  mL/min)
- Uncontrolled or progressive cancer
- Pneumonia or other complex infections
- Treatment with Alemtuzumab
- Mucositis grades 3-4



# DIAGNOSIS OF FEBRILE NEUTROPENIA

Prompt diagnosis is crucial—empirical antibiotic therapy should be initiated within 1 hour of presentation.<sup>1</sup>



## RISK STRATIFICATION TOOLS:<sup>2</sup>

Assessment of risk for complications of severe infection



## LABORATORY TESTS:<sup>2</sup>

CBC with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin



## BLOOD CULTURES:<sup>2</sup>

At least 2 sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing CVC, if present, and from a peripheral vein site



## CULTURE SPECIMENS:<sup>2</sup>

From other sites of suspected infection



## CHEST RADIOGRAPH:<sup>2</sup>

Is indicated for patients with respiratory signs or symptoms

MASCC-score index:

- > 21 → Low risk → Candidates for oral and/or outpatient therapy
- < 21 → High risk → Patient should be admitted to the hospital

ANC of < 500 cells/mm<sup>3</sup> or an ANC that is expected to decrease to < 500 cells/mm<sup>3</sup> during the next 48 hours.

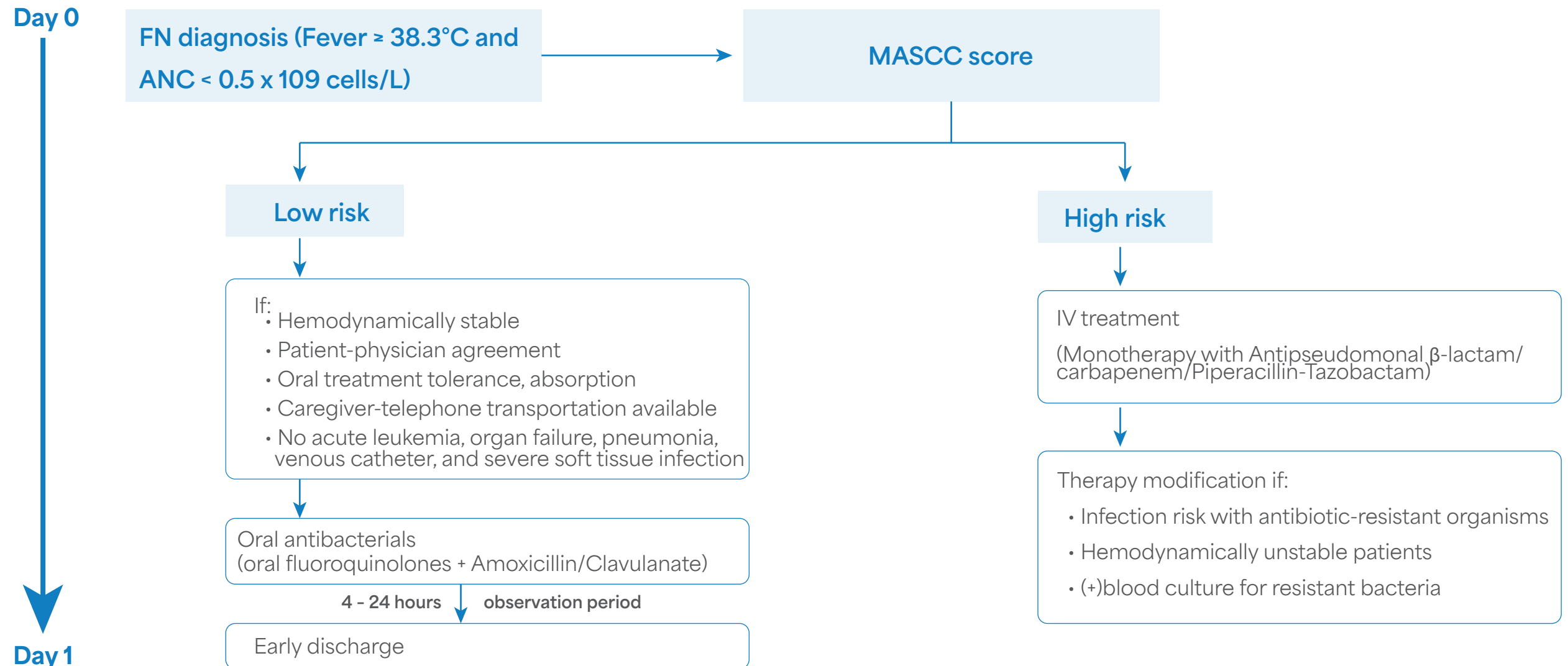
ANC: Absolute Neutrophil Count; CBC: Complete Blood Count; CVC: Central Venous Catheter; MASCC: The Multinational Association of Supportive Care in Cancer.  
 References: 1. Hansen BA, et al. Mediterr J Hematol Infect Dis. 2019;12(1):e2020009. 2. Freifeld AG, et al. Clin Infect Dis. 2011;52(4):e56-93.

SECTION 2:

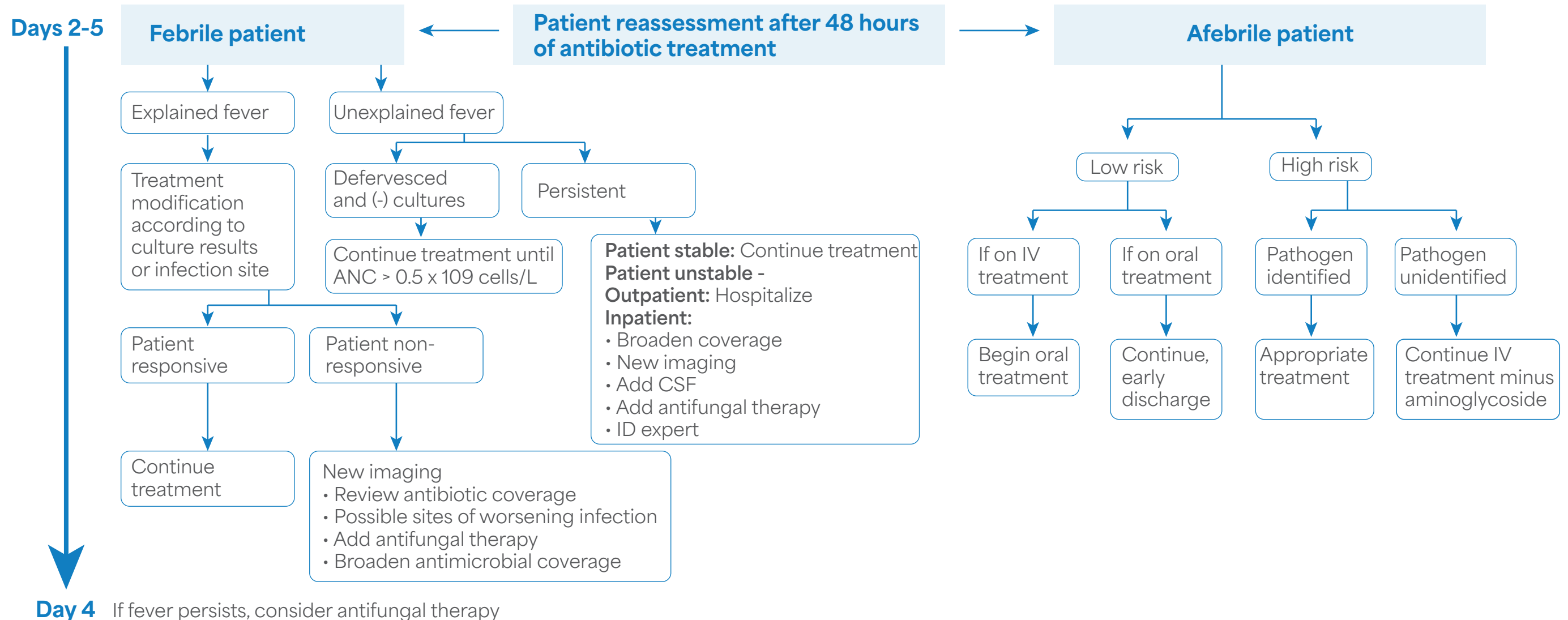
# **MANAGEMENT OF FEBRILE NEUTROPENIA**



# INITIAL ASSESSMENT AND WORKUP FOR CHEMOTHERAPY-INDUCED FEBRILE NEUTROPENIA: EXPERT OPINION



# INITIAL ASSESSMENT AND WORKUP FOR CHEMOTHERAPY-INDUCED FEBRILE NEUTROPENIA: EXPERT OPINION



# RISK-BASED RECOMMENDATIONS FOR FEBRILE NEUTROPENIA



## FN risk $\geq$ 20%

- Start Pegfilgrastim or short-acting G-CSF from cycle 1
- Continue through all chemo cycles  
Evidence level I, 100% consensus



## FN risk 10–20% & FN risk $<$ 10%

- Presence of additional risk factors raises overall FN risk to  $\geq$  20% → give G-CSF  
Evidence level V, 100% consensus

- G-CSF use should be a shared decision between the patient and the physician.
- Once initiated, G-CSF should be continued throughout all chemotherapy cycles.
- Consider patient-, disease-, and treatment-related factors when deciding on G-CSF use.
- Do not withhold G-CSF solely based on a low risk of treatment-related FN.

# ROLE AND TIMING OF ANTIBIOTICS

**Initiate antibiotics immediately after obtaining blood cultures and before completion of other investigations.<sup>1</sup>**  
**Antimicrobial therapy should be administered within 60 minutes of presentation.<sup>1</sup>**

## LOW-RISK PATIENTS<sup>2</sup>

- Maybe given oral antibiotics
- Can be considered for outpatient antibiotics if:  
Closely monitored and live near a hospital for quick access

If fever persists beyond 48 hours, broaden antibiotics and admit the patient to the hospital.



First-line options include:  
Moxifloxacin or Ciprofloxacin  
in combination with  
Amoxicillin/Clavulanic acid  
OR Clindamycin in place  
of Amoxicillin/Clavulanic acid  
in patients allergic to  
Penicillin.



## HIGH-RISK PATIENTS<sup>2</sup>

- Inpatient admission and IV antibiotics are indicated
- Institutional susceptibility patterns should be considered when selecting therapy.

If no response to initial therapy, broaden antimicrobial coverage to include resistant pathogens, anaerobes, and fungi.



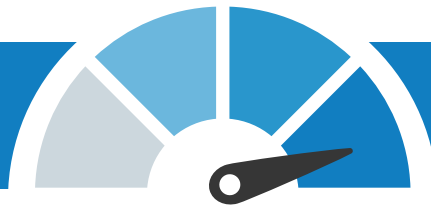
High-risk patients will need to receive an antipseudomonal  $\beta$ -lactam agent such as:  
→ Cefepime  
→ Piperacillin-Tazobactam  
→ Meropenem  
→ Imipenem/Cilastatin



**In all cases, continue treatment until the ANC is  $\geq 500$  cells/mm<sup>3</sup> and the patient is afebrile for at least 48 hours.**

# ANTIBIOTIC DECISION TREE: HIGH-RISK FEBRILE NEUTROPENIA

## High-risk patients



- Need to be hospitalized
- Institutional susceptibility patterns should be considered
- *Pseudomonas* is the main target during initial empiric therapy
- Antipseudomonal  $\beta$ -lactam agent required

*Vancomycin is recommended as an empiric treatment for specific indications, including skin/soft tissue infections, pneumonia, catheter-related infections, or patients who are hemodynamically unstable.*

## Treatment options for resistant pathogens:

MRSA: Vancomycin, Linezolid, and  
Daptomycin

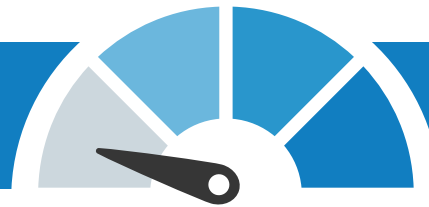
VRSA: Linezolid and Daptomycin

ESBL: Carbapenems (Meropenem)

KPC: Colistin, Tigecycline

# ANTIBIOTIC DECISION TREE: LOW-RISK FEBRILE NEUTROPENIA

## Low-risk patients



- Carefully selected for outpatient antibiotics, BUT
- Monitor closely for clinical deterioration
- Must be located within a reasonable distance to a hospital

*If a patient remains febrile for 48 hours, antibiotic coverage should be broadened, and the patient will need to be admitted to the hospital.*



## First-line options →

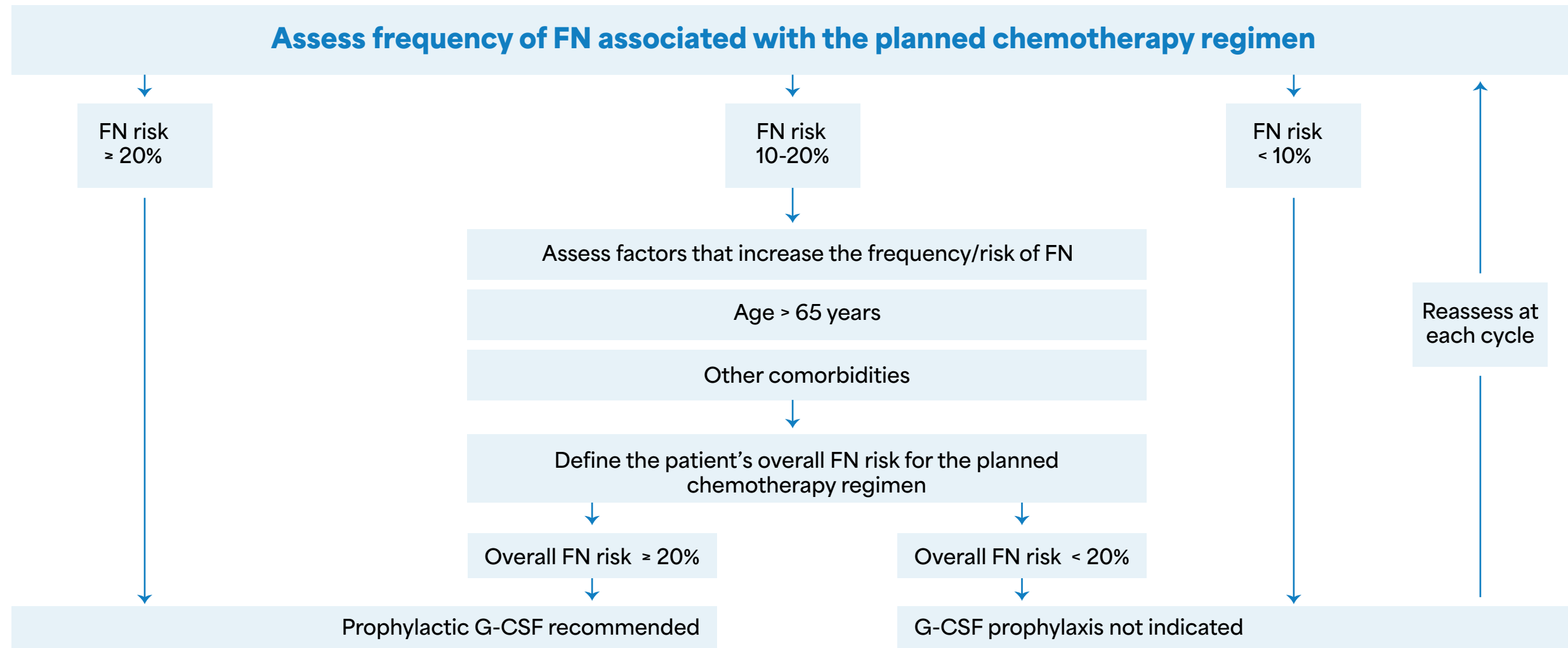
Fluoroquinolone monotherapy  
(Moxifloxacin or Ciprofloxacin +  
Amoxicillin/Clavulanic acid)

## Patients with penicillin allergies →


Use Clindamycin



# ALGORITHM TO DECIDE PRIMARY PROPHYLACTIC G-CSF USAGE



# MANAGEMENT OF FEBRILE NEUTROPENIA: ICMR 2022 GUIDELINES

	Clinical Condition	Empirical Antimicrobial Agents	Alternate Antimicrobial Agents
	FN	Piperacillin-Tazobactam + Amikacin	<ul style="list-style-type: none"><li>• <b>First-line:</b> Piperacillin-Tazobactam + Amikacin</li><li>• <b>Second-line:</b> Meropenem ± Teicoplanin/Vancomycin</li><li>• <b>Third-line or if patient is in septic shock:</b> Meropenem + Colistin/Polymyxin B ± Teicoplanin/Vancomycin + Caspofungin ± Fosfomycin/Tigecycline</li></ul>

# OUTPATIENT EMPIRIC THERAPY IN FEBRILE NEUTROPENIA: IDSA GUIDELINES

What antimicrobials are recommended for outpatient empirical therapy in patients with FN?

01

## RECOMMENDATION FOR ORAL EMPIRICAL THERAPY:

Fluoroquinolone (Ciprofloxacin or Levofloxacin) plus Amoxicillin/Clavulanate (or Clindamycin for patients allergic to Penicillin)

02

In a high prevalence setting of **ESBL-PRODUCING GRAM-NEGATIVE BACILLI OR FLUOROQUINOLONE RESISTANCE:**

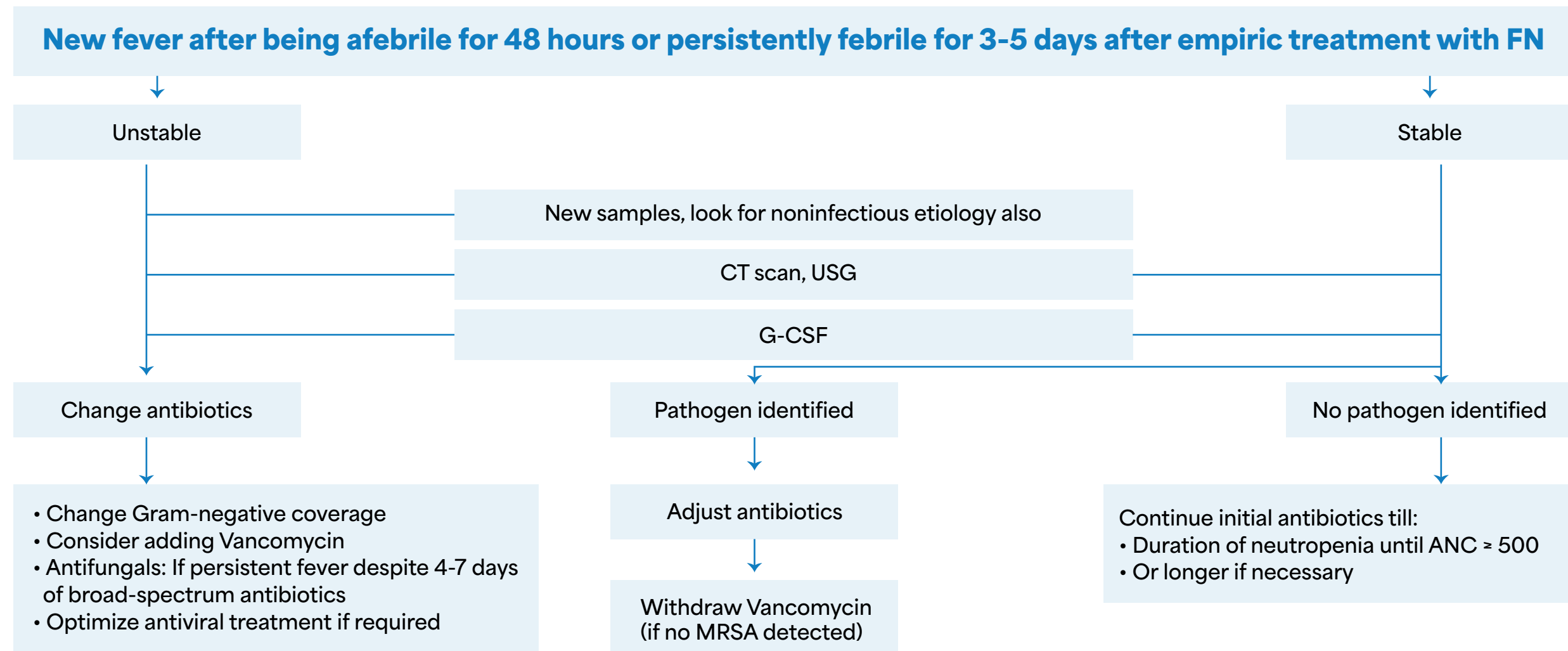
Hospital admission and consider initial empirical antibacterial treatment with a carbapenem

03

**MRSA, VRE, concern for specific active infection or CRBSI:**

Hospital admission and consider targeted therapy

# APPROACH TO NEW-ONSET FEVER AFTER 48 HOURS OR PERSISTENT FEVER IN FEBRILE NEUTROPENIA



# SECTION 3:

## **ROLE OF BL/BLIs IN FEBRILE NEUTROPENIA**

# ROLE OF BL/BLIs AS EMPIRIC THERAPY IN FEBRILE NEUTROPENIA

01

## ECIL-10 RECOMMENDATIONS (2024):

- Piperacillin-Tazobactam (a BL/BLI) is listed as a first-line empiric antibiotic option for patients with FN.
- Other BL/BLIs such as Ticarcillin-Clavulanate and Cefoperazone-Sulbactam are also mentioned as possible empiric options.

02

## GUIDELINES EMPHASIZE USING BL/BLIs IN:

- Uncomplicated presentation
- No known colonization with resistant bacteria
- No previous infection with resistant bacteria
- In centers where infections due to resistant pathogens are rarely seen at the onset of FN

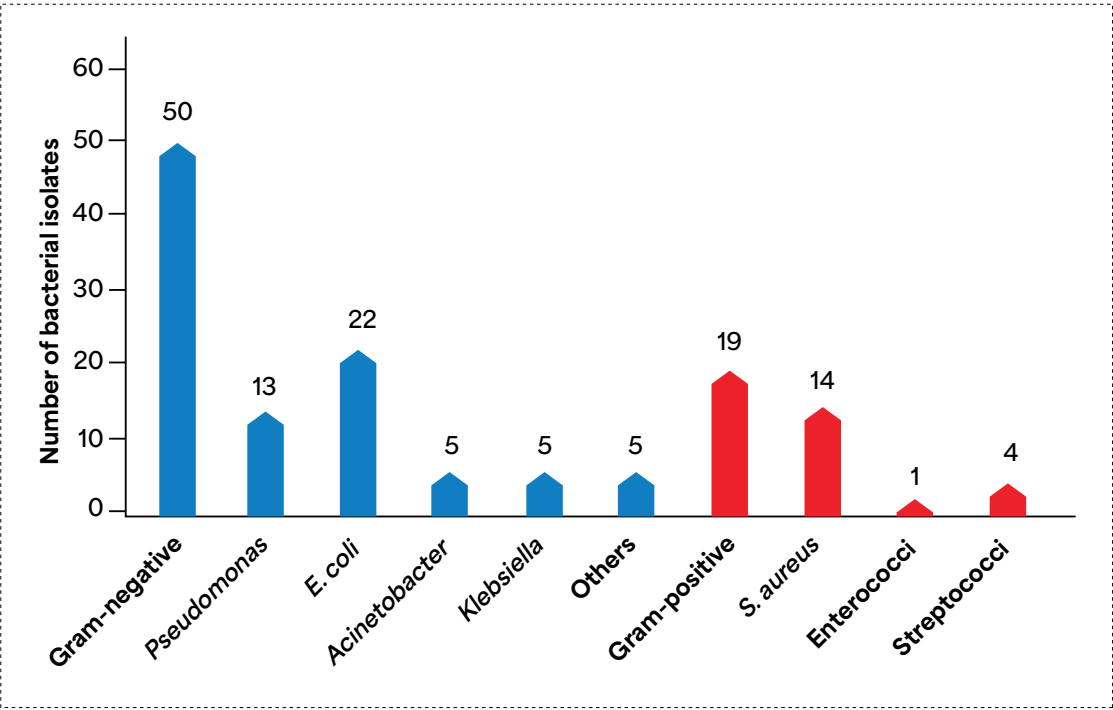
**These findings favor the use of BL/BLIs in the empiric treatment of FN.**

# LOCAL ANTIBIOGRAM DATA SUPPORTING BL/BLI USE

Retrospective analysis of patients presenting with FN to a tertiary care oncology hospital in India

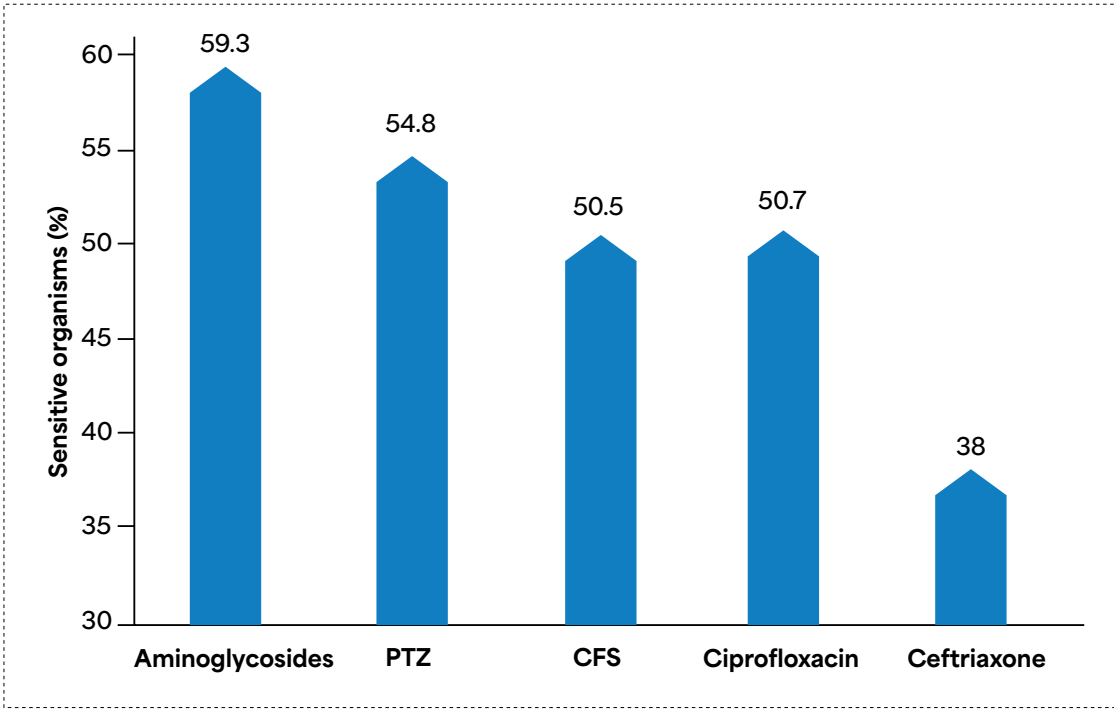
93% of patients treated with third-generation cephalosporin/BLI, with aminoglycoside or fluoroquinolone.

Bacterial isolates identified in blood



Predominant cause of FN: **Gram-negative bacteremia**

Antibiotic sensitivity of isolates

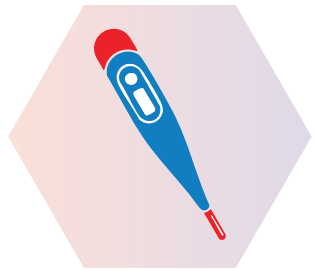


Most commonly used antibiotic combination: **CFS**

BL/BLI:  $\beta$ -Lactam/ $\beta$ -Lactamase Inhibitor; CFS: Cefoperazone-Sulbactam; FN: Febrile Neutropenia; PTZ: Piperacillin-Tazobactam.  
Reference: 1. Noronha V, et al. Indian J Cancer. 2014;51(4):470-4.

# AN INDIAN STUDY ON THE PREVALENCE OF CARBEPENEM-RESISTANT INFECTIONS IN PATIENTS WITH FEBRILE NEUTROPENIA

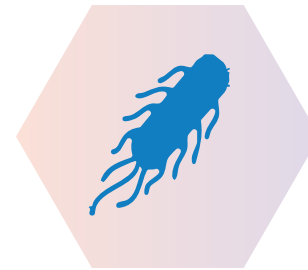
The bacterial spectrum and prevalence of antimicrobial resistance in bloodstream infections in adult patients with FN having hematolymphoid malignancies in a tertiary oncology center in India.



**307 out of 1670**  
patients with  
hematolymphoid  
malignancies had FN



**Microbiologically confirmed**  
bloodstream  
infections: **24.1%**



Most common  
organism:  
***E. coli* (36.4%)**



**Carbapenem-resistant** Gram-  
negative  
bloodstream  
infections: **38.2%**



**Mortality rate: 32.6%**

**Use of BL/BLIs as carbapenem-sparing alternatives may be useful to avoid the spread of CRE.  
This strategy may prove useful in limiting the spread of carbapenem resistance.**



# EMPIRIC USE OF CEFOPERAZONE-SULBACTAM IN FEBRILE NEUTROPENIA

A meta-analysis assessed the clinical efficacy and safety of Cefoperazone-Sulbactam for treating FN.



## **Treatment success rate:**

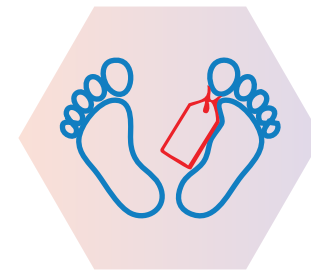
57.9%

Similar to comparators\*



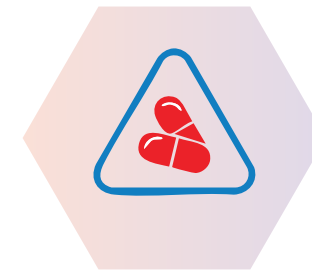
## **Similar treatment success rate →**

Piperacillin-Tazobactam and carbapenems



## **All-cause mortality:**

6% Similar to comparators\*



## **Most common adverse events:**

Rash and nausea/vomiting  
Similar to comparators\*

**The clinical efficacy and tolerability of Cefoperazone-Sulbactam are comparable to comparator drugs in the treatment of FN.**

FN: Febrile Neutropenia.

\*Four studies used Piperacillin-Tazobactam as the comparator and 4 used carbapenems. One study each used Cefepime, Cefoperazone plus Mezlocillin, and Ceftazidime as the comparator.

Reference: 1. Lan SH, et al. Medicine (Baltimore). 2020;99(8):e19321.

# PIPERACILLIN-TAZOBACTAM VS. CEFOPERAZONE-SULBACTAM IN FEBRILE NEUTROPENIA

A study compared the efficacy of PTZ and CFS in adult patients with hematological malignancies in FN

## Study design -

### Sample size:

157 patients, 200 episodes of FN

### Patient characteristics:

- > 18 years old
- ANC < 500/mm<sup>3</sup>
- Oral body temperature > 38.3°C at a single measurement or 38°C after 1-h monitoring

## Results

**44.5%**

Microbiologically documented infections

**61%**

Overall success rate with CFS → Similar to PTZ (41%)

**26.8%**

Success rate without modification (CFS) → Similar to PTZ (22.9%); similar trend observed with success rate with modification

**14%**

Mortality rate with CFS → Similar to PTZ (16.9%)

**PTZ and CFS are equally effective and safe for the empirical treatment of patients with FN.**

# REAL-WORLD EVIDENCE

**Objective: To compare the effectiveness of  $\beta$ -lactam empiric therapy in patients with FN.**

## Study details -

### Study design:

Systematic review and meta-analysis

### Patients:

Adult and pediatric patients with FN undergoing chemotherapy for either solid tumors or hematological malignancies

### Analysis:

1275 articles, 50 studies, 10872 patients

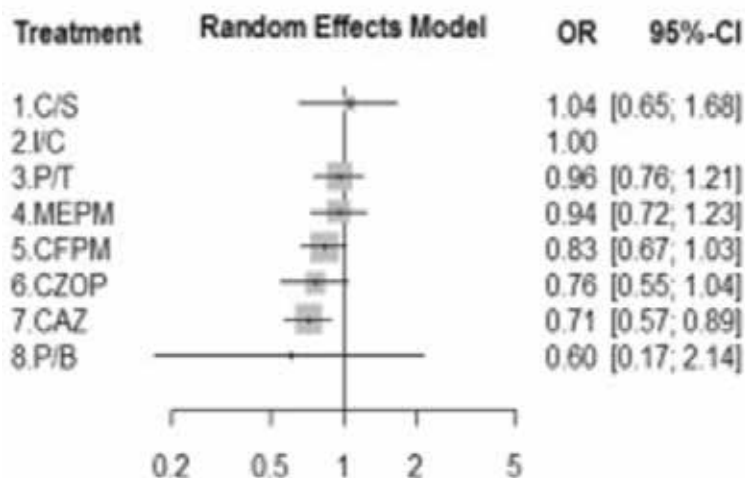
## Results



### Cefoperazone-Sulbactam:

Highest odds for treatment success followed by Imipenem/Cilastatin and Piperacillin-Tazobactam

### Treatment success without modification



**Cefoperazone-Sulbactam: An effective alternative in the empiric treatment of FN.**

SECTION 4:  
**CASE DISCUSSION**



# CASE 1: FEBRILE NEUTROPENIA IN A PEDIATRIC CANCER PATIENT

## Patient profile

- Age: 20-year-old male
- Chief complaint: Episodic fevers
- Medical history:
  - Burkitt leukemia
  - Previously hospitalized (3 weeks prior to current presentation) for similar symptoms, reduced ANC, which recovered with supportive care
  - After discharge: Normal complete blood counts (taken weekly)

## History of present illness

- Regular episodic fevers for the past 6 months
- Frequency of episodic fevers: 4–6 weeks (but has been increasing in frequency in the past 2 months)
- Duration of episodic fevers: 3 days
- Temperature: 103°F
- Additional symptoms: Muscle pain and occasionally sore throat, chills, night sweats, decreased appetite, and unintended weight loss of 5–10 kg

## How to proceed with the medical management of this patient?

**Points for discussion:** 1. Choice of antibiotic 2. Role of BL/BLI – dosage, duration of therapy 3. Escalation/de-escalation of antibiotics

# CASE 2: FEBRILE NEUTROPENIA IN AN IMMUNOCOMPROMISED ADULT PATIENT

## Patient profile

**Age:** 68-year-old male

**Chief complaint:** Persistent daily fever

**Medical history:** Stage IVB diffuse large B-cell lymphoma (DLBCL)

### Clinical examination:

- 9 × 3 cm sized hematoma on the left upper extremity at the site of IV infiltration from a previous hospitalization
- Healing Stage II decubitus ulcer
- Temperature: 102.9°F

## Investigations

- Hemoglobin: 7.4 g/dL
- Leukocyte count:  $0.4 \times 10^9/L$
- Platelet count:  $12 \times 10^9/L$
- Alkaline phosphatase: 275 U/L
- Creatinine: 0.6 mg/dL
- Lactate dehydrogenase: 229 U/L
- Normal levels of:
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Total bilirubin

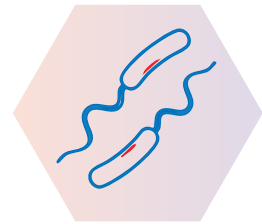
## How to proceed with the medical management of this patient?

**Points for discussion:** 1. Choice of antibiotic 2. Role of BL/BLI – dosage, duration of therapy 3. Escalation/de-escalation of antibiotics

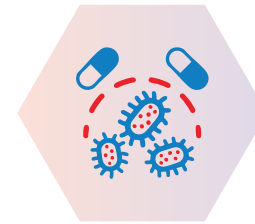
# **SUMMARY AND KEY TAKEAWAYS**



# KEY TAKEAWAYS



**Gram-negative infections** predominantly cause FN in Indian patients.



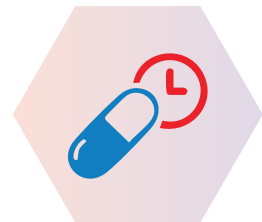
The growing threat of carbapenem resistance highlights the role of **BL/BLIs as an effective alternative**.



**Prompt diagnosis is essential** and risk assessment tools are critical for guiding appropriate treatment decisions.



**Cefoperazone-Sulbactam offers comparable effectiveness** and tolerability to standard treatments for FN.



**Timely administration of antibiotics**—ideally within 1 hour of presentation—is vital in the management of FN.



**THANK YOU!**

