
بسم الله الرحمن الرحيم

Fever in children with chemotherapy-induced neutropenia

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INTRODUCTION

- — **Infection is a major cause of morbidity and mortality in cancer patients .**
- Fever may be the first manifestation of a life-threatening infection, particularly during periods of neutropenia.
- Febrile episodes occur in approximately one-third of neutropenic episodes in children with chemotherapy-induced neutropenia .

DEFINITIONS

- **Neutropenia**
- For purposes of management of the febrile pediatric cancer patient, neutropenia is defined as an ANC <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL during the next 48 hours .
- The relative risk of infection is related to both the degree and duration of neutropenia.

DEFINITIONS

- **Fever**
- **FEVER: > 38.3°C once OR > 38°C for ≥ 1 hour OR two temperatures > 38°C within 12 hours**
- Oral temperature measurements are preferred, although an axillary temperature is acceptable if the patient is unable to use an oral thermometer.
- *Generally, no conversion is made between axillary and oral temperatures*. However, more conservative guidelines suggest that adding 0.5°F (0.3°C) to the axillary temperature reading may be warranted.
- If the axillary thermometer does not automatically adjust, some centers consider fever as a single axillary temperature of ≥37.7°C (99.9°F) or axillary temperature ≥37.4°C (99.4°F) for longer than one hour
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DEFINITIONS

- Fever often is the sole sign of occult infection in the neutropenic host .
- However, this sign may be absent in some infected patients who instead may be *hypothermic, hypotensive, listless, or confused*.
- Similarly, infected children who are receiving glucocorticoids may present with a lower and/or intermittent temperature elevation – or may be afebrile.

Neutropenic fever syndromes

- Microbiologically documented infection – Neutropenic fever with a clinical focus of infection and an associated pathogen
- Clinically documented infection – Neutropenic fever with a clinical focus (eg, cellulitis, pneumonia) but without the isolation of an associated pathogen
- Unexplained fever – Neutropenic fever with neither a clinical focus of infection nor an identified pathogen

Risk category

- — Patients with fever and neutropenia can be divided into high- and low-risk categories based upon:
- *presenting signs and symptoms,*
- *ANC,*
- *underlying cancer,*
- *type of therapy and the anticipated length of neutropenia,*
- *medical comorbidities .*

Risk category

- **High-risk** — High-risk patients have an increased risk of severe infection.
- **Patients with any of the following should be considered as high-risk**
- ●Neutropenia (ANC <500 cells/microL) anticipated to last >7 days. *Although the 2010 (IDSA) guidelines define patients as high-risk if they have profound neutropenia (ANC ≤100 cells/microL) anticipated to last >7 days ,*
- we have opted to define high-risk as neutropenia (ANC <500 cells/microL) anticipated to last >7 days.

Risk category

- Evidence of hepatic insufficiency (aminotransferase levels >5 times normal values)
- renal insufficiency (creatinine clearance <30 mL/min)
- Comorbid medical problems including, but not limited to:
- Hemodynamic instability
- Oral or gastrointestinal mucositis that interferes with swallowing or causes diarrhea

Risk category

- Gastrointestinal symptoms, including abdominal pain, nausea, vomiting, or diarrhea
- •New-onset neurologic or mental status changes
- •Intravascular catheter infection (especially catheter tunnel infection)
- •New pulmonary infiltrate or hypoxemia or underlying chronic lung disease
- ●Patients with infant acute lymphoblastic leukemia, acute myeloid leukemia, or within 30 days of hematopoietic cell transplant

Risk category

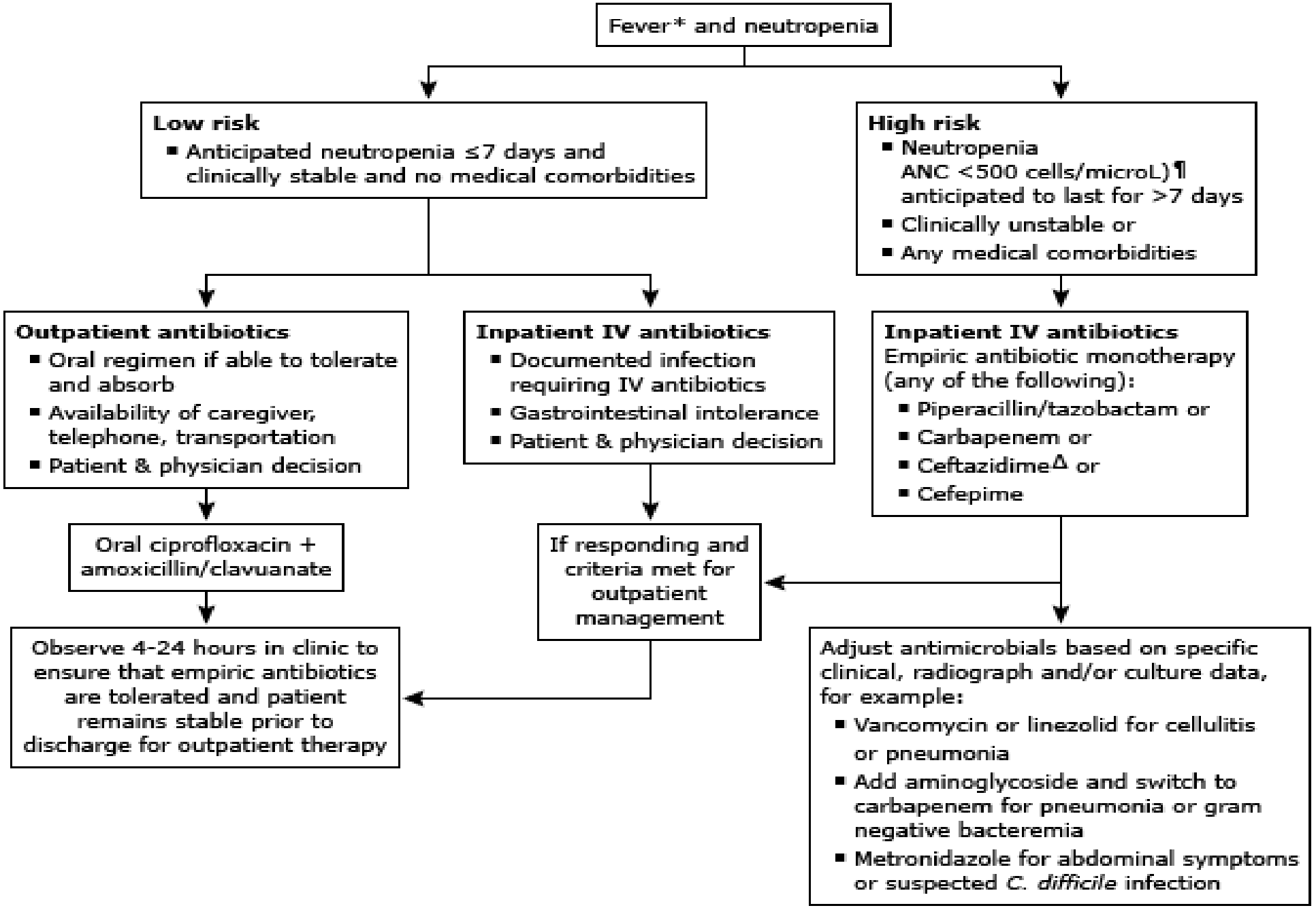
- any localising symptoms such as central nervous system, pulmonary, gastrointestinal (especially mucositis),
- CVC site symptoms such as erythema or swelling increase the risk.
- progressive disease; or treatment for relapsed disease with marrow involvement
- neutrophil count less than $0.1 \times 10^9/L$
- fever>24h
- fever>39 ˚C
- Any positive culture

Risk category

- **Low-risk** — Low-risk patients are those with :
- ●Neutropenia expected to resolve within seven days
- ●Stable and adequate hepatic and renal function
- ●No active comorbidities
- Carefully selected low-risk patients may be candidates for oral empiric therapy or outpatient treatment.

Risk category

- High-risk patients should be admitted to the hospital for empiric antimicrobial therapy
    - algorithm .


Fever* and neutropenia
Low risk
Anticipated neutropenia ≤7 days and clinically stable and no medical comorbidities
High risk
Neutropenia ANC <500 cells/microL)¶ anticipated to last for >7 days
Clinically unstable or
Any medical comorbidities
Outpatient antibiotics
Oral regimen if able to tolerate and absorb
Availability of caregiver, telephone, transportation
Patient & physician decision
Inpatient IV antibiotics
Documented infection requiring IV antibiotics
Gastrointestinal intolerance
Patient & physician decision
Inpatient IV antibiotics
Empiric antibiotic monotherapy (any of the following):
Piperacillin/tazobactam or
Carbapenem or
Ceftazidime∆ or
Cefepime
Oral ciprofloxacin + amoxicillin/clavuanate
If responding and criteria met for outpatient management
Observe 4-24 hours in clinic to ensure that empiric antibiotics are tolerated and patient remains stable prior to discharge for outpatient therapy
Adjust antimicrobials based on specific clinical, radiograph and/or culture data, for example:
Vancomycin or linezolid for cellulitis or pneumonia
Add aminoglycoside and switch to carbapenem for pneumonia or gram negative bacteremia
Metronidazole for abdominal symptoms or suspected C. difficile infection

ETIOLOGY OF FEVER

- — The rate of documented infection, ranges between 10 and 40 percent .
- No clinical or microbiologic evidence of infection will be established in the remainder.
- *Bacteremia is the most common form of documented infection* .
- Other sites of infection include :
- *Gastrointestinal tract, with oral or intestinal mucositis or diarrhea caused by Clostridium difficile and Salmonella spp;*
- *Upper and lower respiratory tract;*
- *Urinary tract;*
- *Skin and soft tissues .*

ETIOLOGY OF FEVER

- Both gram-positive and gram-negative organisms are isolated frequently from the blood in febrile neutropenic children .
- In general, there is a global shift toward a dominance of gram-positive organisms due to the ubiquitous use of prophylactic antimicrobials and indwelling venous catheters.

ETIOLOGY OF FEVER

- The most common gram-positive pathogens are coagulase-negative staphylococci, viridans streptococci, and *Staphylococcus aureus* (including MRSA) .
- Aerobic gram-negative bacilli account for approximately one-third to one-half of bacteremic episodes, with *Escherichia coli*, *Klebsiella* spp, *Pseudomonas* spp, *Acinetobacter* spp, and *Enterobacter* spp among the more common isolates .

ETIOLOGY OF FEVER

- Fungi, typically *Candida* spp, are more likely to be recovered after prolonged courses of broad-spectrum antibiotics but occasionally may be the primary pathogen .
- Other potential fungal organisms include *Aspergillus* spp, *Zygomycetes*, and *Cryptococcus* spp .
- The most significant viral etiologies are herpes simplex and varicella-zoster virus .

EVALUATION

- Serious infection may occur in the absence of fever and/or neutropenia and must be considered in the pediatric cancer patient who is febrile and neutropenic; febrile but not neutropenic; or neutropenic and afebrile with signs of infection or clinical deterioration .
- Prompt initiation of empiric therapy can be life-saving, *so rapid (but thorough) evaluation is critical.*

EVALUATION

- **History** — Important aspects of the history :
- ●New site-specific symptoms
- ●Antimicrobial prophylaxis
- ●Infection exposures
- ●History of documented infections or colonization
- ●Concomitant noninfectious cause of fever (eg, receipt of blood products)
- ●Underlying comorbid conditions (eg, diabetes, recent surgery)
- ●Previous chemotherapy, agents used, and the stage of therapy (to anticipate the length of the neutropenic episode)
- ●Intravascular catheters or other devices

EVALUATION

- **Physical examination** —
- ●Abnormal vital signs, particularly tachycardia (even without hypotension)
- ●Skin, especially folds, areas surrounding nail beds, central venous line exit sites and subcutaneous tunnel, if present, and sites of bone marrow aspiration and lumbar puncture
- ●Sinuses
- ●Oropharynx, with attention to the gingiva
- ●Lungs
- ●Abdomen
- ●Perineum, particularly the perianal and labial regions

EVALUATION

- **Laboratory tests and imaging**
- ●Complete blood count
- ●Electrolytes, creatinine, and BUN
- ●Liver transaminases and total bilirubin
- ●Blood cultures
- CRP
- U/A,U/C

EVALUATION

- Blood cultures should be obtained without delay.
- Blood cultures should be taken from each lumen of the central line when such access is available .
- A catheter-related bloodstream infection can be diagnosed if the colony count of microbes in blood obtained via the catheter hub is at least threefold greater than that obtained from the peripheral blood or if the culture obtained via the catheter hub becomes positive at least two hours before the peripheral blood when using a continuous read system.

EVALUATION

- If the child remains febrile after initiation of empiric antibiotic therapy, daily blood cultures should be obtained for the next two days.
- Blood cultures also should be repeated if fever recurs following initial defervescence in response to empiric antibiotic therapy.
- In one study, urinary tract infections accounted for 11 percent of all documented infections in febrile neutropenic patients, and 76 percent of those occurred in girls .

OVERVIEW OF TREATMENT

- — The cornerstone of therapy for the febrile, neutropenic patient is *prompt initiation of empiric broad-spectrum antibiotics.*
- In an observational study in pediatric cancer patients, receipt of antibiotics within 60 minutes of presentation was associated with decreased rates of ICU consultation or admission among .

Empiric antimicrobial therapy

- The guidelines emphasize that, when choosing empiric therapy, each practitioner should consider :
- ●Whether the child is at high or low risk of infection
- ●Drug allergies of the patient,
- ●Presence of organ dysfunction, particularly renal and hepatic
- ●The particular chemotherapeutic regimen and when it was administered: for example, an association exists between viridans streptococcal infection and high-dose cytarabine therapy
- ●Whether the patient was receiving prophylactic antimicrobials
- ●Previous colonization with resistant bacteria (eg, [MRSA]; vancomycin-resistant enterococcus; extended-spectrum beta-lactamase producing organism, including *Klebsiella pneumoniae* carbapenemase)

Empiric antimicrobial therapy

- **Initial therapy**
- **Suggested regimens** — Initial therapy with a broad-spectrum antipseudomonal beta-lactam (eg, cefepime or ceftazidime), a carbapenem (eg, meropenem), or piperacillin-tazobactam is recommended for uncomplicated episodes of fever in neutropenic patients .
- Randomized controlled trials and systematic reviews have demonstrated that empiric monotherapy with these agents is as efficacious as combination therapy but with fewer adverse events .

Empiric antimicrobial therapy

- Recommended agents include:
- ●Cefepime – 50 mg/kg intravenously (IV) every 8 hours up to a maximum of 2 g per dose; adjust dose for renal dysfunction; **OR**
- ●Ceftazidime – 50 mg/kg IV every 8 hours up to a maximum of 2 g per dose; adjust dose for renal dysfunction; **OR**
- ●Meropenem – For children ≥3 months of age: 20 mg/kg IV every 8 hours up to a maximum of 1 g per dose for non-central nervous system infections and 40 mg/kg IV every 8 hours up to a maximum of 2 g/dose for central nervous system infections; adjust dose for renal dysfunction; **OR**

Empiric antimicrobial therapy

- Ceftazidime is no longer recommended for empiric monotherapy in high-risk patients because of increased resistance among many gram-negative pathogens and weak activity against viridans streptococci.

Empiric antimicrobial therapy

- ●Piperacillin-tazobactam – For infants and children <30 kg: 100 mg/kg of piperacillin component IV every 6 to 8 hours; for children ≥30 kg: 3 g of piperacillin component IV every 6 hours; the maximum daily dose of the piperacillin component is 16 g/day;
- If a carbapenem is to be used, meropenem is preferred because of the risk of seizures with imipenem-cilastatin.

Empiric antimicrobial therapy

- Additional antimicrobials may be added to the initial regimen based on the clinical presentation, suspected antimicrobial resistance, or for management of complications.
- As an example, if abdominal symptoms are present, particularly *abdominal pain or blood per rectum*, metronidazole should be added if the initial combination does not adequately cover anaerobic organisms
- Likewise, if infection with MRSA is suspected, the addition of vancomycin may be beneficial.

Empiric antimicrobial therapy

- **Vancomycin —**
- Vancomycin is not routinely recommended in the initial empiric regimen for patients with fever and neutropenia .
- It should be reserved for children with clear indications for additional gram-positive coverage.

Empiric antimicrobial therapy

- Although up to two-thirds of bacterial isolates from blood in febrile neutropenic cancer patients are gram-positive cocci, frequently coagulase-negative staphylococci resistant to extended-spectrum penicillins or third-generation cephalosporins, the morbidity and mortality have not differed in patients treated with or without vancomycin in the initial antibiotic regimen.
- Infections with alpha-hemolytic streptococci may be an exception to this observation .

Empiric antimicrobial therapy

- The 2010 guidelines from the IDSA recommend that vancomycin be reserved for the following clinical scenarios :
- ●Hypotension or other signs of cardiopulmonary deterioration
- ●Radiographically documented pneumonia
- ●Clinically suspected central venous line site infection (eg, chills or rigors with infusion through the catheter and cellulitis around the catheter entry or exit site)
- ●Skin or soft tissue infection at any site
- ●Known colonization with MRSA, penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*
- ●When a blood culture has been reported to be growing gram-positive bacteria and identification and susceptibility testing are pending

Empiric antimicrobial therapy

- Additional indications for vancomycin may include:
- ●Substantial mucositis
- ●Prophylaxis with quinolones during afebrile neutropenia
- ●Recent intensive chemotherapy associated with a high risk for infection with such organisms (eg, alpha-hemolytic streptococcal infection following high-dose cytarabine)
- If vancomycin is added to the empiric regimen for one of the above indications and susceptible bacteria are not recovered from the patient within two to three days, vancomycin should be discontinued

Empiric antimicrobial therapy

- **Aminoglycosides** — are not recommended for initial therapy for febrile neutropenic cancer patients.
- However, they may be added to the initial regimen in the presence of complications (eg, hypotension and pneumonia) or if there is a suspicion of antimicrobial resistance .
- Aminoglycoside monotherapy should not be used either as empiric coverage or treatment because of the rapid development of resistance.

Outpatient therapy

- — Outpatient management of fever and neutropenia with IV or oral antibiotics may be an option for carefully selected low-risk patients if daily follow-up is ensured .
- When children with fever and chemotherapy-induced neutropenia are treated as outpatients, they should receive the *first dose of antimicrobial therapy in a clinical or hospital setting and be observed for ≥4 hours before discharge .*
- They should **be readmitted** for hemodynamic instability, signs and symptoms of new or worsening infection, or, in the absence these, persistent fever (ie, >48 to 96 hours).

Outpatient therapy

- A systematic review of four randomized trials comparing inpatient and outpatient treatment for children with cancer and low-risk febrile neutropenia found no clear evidence of different rates of treatment failure, mortality, or adverse drug reactions.
- However, outpatient treatment in these trials consisted of early discharge after surveillance for 24 to 72 hours rather than exclusive outpatient therapy .

Outpatient therapy

- •**Criteria**
- – Outpatient oral therapy is an option for children who meet all of the following criteria :
- -Able to take and absorb oral antibiotics
- -Has a caregiver and a telephone
- -Live relatively close to their local medical facility in the event of clinical worsening (eg, within one hour)
- -Able to adhere to daily outpatient follow-up
- -Patient or caregiver(s) and clinician agree to oral outpatient therapy
- -Has not been receiving fluoroquinolone prophylaxis

Outpatient therapy

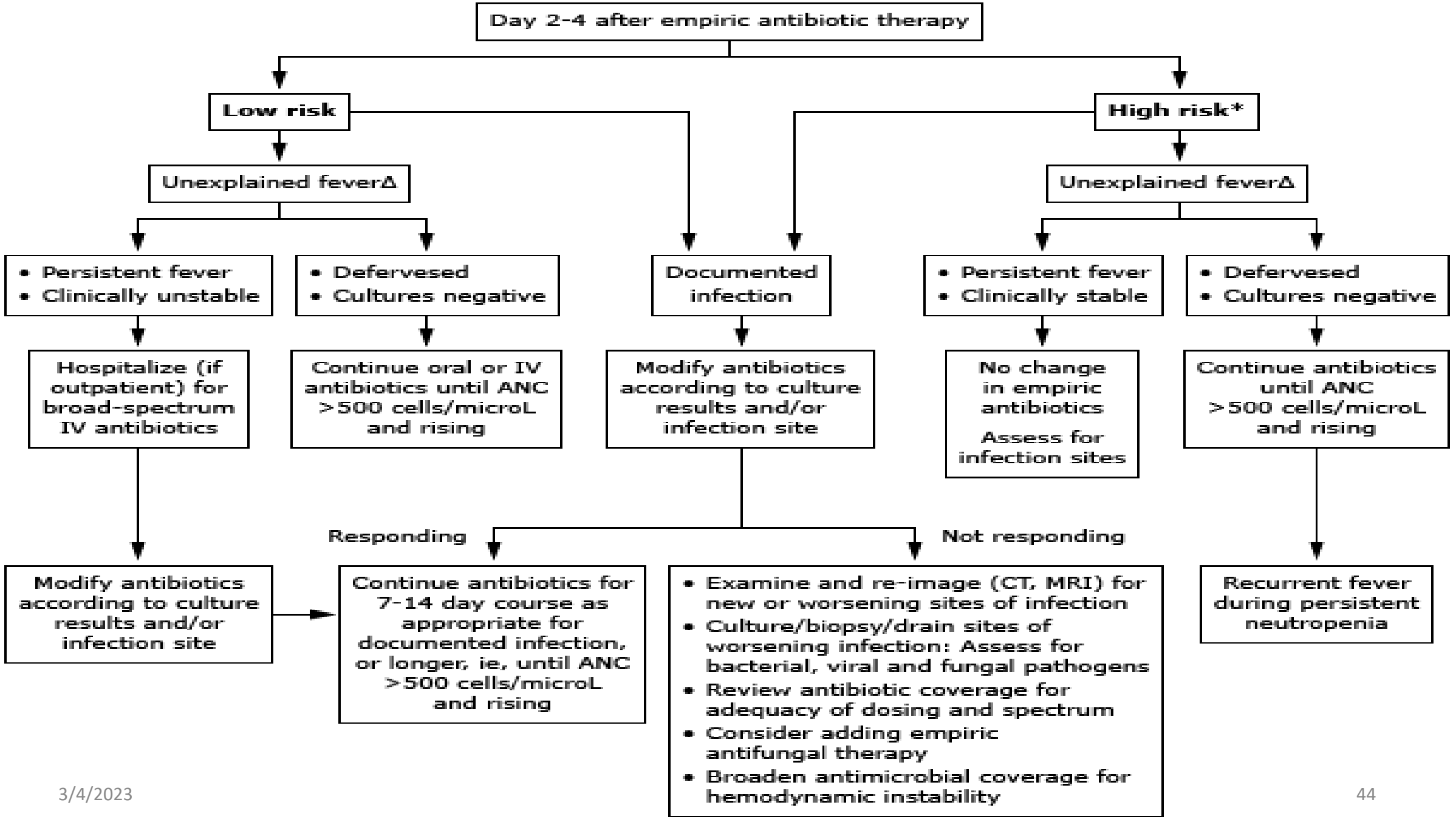
- •**Oral regimen** – For low-risk children who receive oral outpatient therapy and have not been receiving fluoroquinolone prophylaxis, we suggest oral empiric therapy with ciprofloxacin plus amoxicillin-clavulanate rather than other oral regimens .
- Although this regimen has not been well-studied in children, it appears to be as effective as IV therapy in low-risk patients .

Outpatient therapy

- In two randomized trials, the rate of treatment failure and duration of fever, neutropenia, and antimicrobial therapy were similar in patients treated with oral ciprofloxacin/amoxicillin-clavulanate versus IV ceftriaxone or cefepime .
- There are few data to guide the choice of outpatient regimen for low-risk children with contraindications to ciprofloxacin combined with amoxicillin-clavulanate or low-risk children who have been receiving fluoroquinolone prophylaxis.
- Consultation with an expert in infectious diseases is suggested to optimize the regimen for individual patients.
- Hospitalization for IV therapy may be necessary.

Empiric antimicrobial therapy

- **Modifications of initial therapy** — Modification of the regimen may be warranted based upon a variety of clinical scenarios, including (algorithm 2) ;
- ●Change in clinical status or vital signs
- ●Isolation of a blood-borne organism
- ●Documented clinical or microbiologic infection
- ●Development of signs or symptoms of a localized infection
- ●Persistent fever for more than four days (algorithm 3)
- ●Recurrent fever after initial defervescence


Day 2-4 after empiric antibiotic therapy
Low risk
High risk*
Unexplained feverΔ
Unexplained feverΔ
• Persistent fever
• Clinically unstable
• Defervesed
• Cultures negative
Documented infection
• Persistent fever
• Clinically stable
• Defervesed
• Cultures negative
Hospitalize (if outpatient) for broad-spectrum IV antibiotics
Continue oral or IV antibiotics until ANC >500 cells/microL and rising
Modify antibiotics according to culture results and/or infection site
No change in empiric antibiotics
Assess for infection sites
Continue antibiotics until ANC >500 cells/microL and rising
Responding
Not responding
Modify antibiotics according to culture results and/or infection site
Continue antibiotics for 7-14 day course as appropriate for documented infection, or longer, ie, until ANC >500 cells/microL and rising
• Examine and re-image (CT, MRI) for new or worsening sites of infection
• Culture/biopsy/drain sites of worsening infection: Assess for bacterial, viral and fungal pathogens
• Review antibiotic coverage for adequacy of dosing and spectrum
• Consider adding empiric antifungal therapy
• Broaden antimicrobial coverage for hemodynamic instability
Recurrent fever during persistent neutropenia

Antifungal therapy

- — Fungi are not often isolated as the initial cause of fever and neutropenia but are often in the differential diagnosis of persistent or recurrent fever.
- Clinically occult fungal infection must be considered in children with persistent fever (ie, ≥4 days) and neutropenia despite empiric antibacterial therapy .

Antifungal therapy

- Additional risks for invasive fungal infection include:
- acute myeloid leukemia,
- relapsed acute leukemia,
- high-risk acute lymphoblastic leukemia,
- prolonged neutropenia (>10 days),
- highly myelosuppressive chemotherapy,
- high-dose glucocorticoids (usually defined as prednisone ≥20 mg per day, or >2 mg/kg per day for patients weighing <10 kg) for ≥14 days
- Allogeneic hematopoietic cell transplant recipients .

Antifungal therapy

- The 2010 IDSA guidelines and the 2017 International Pediatric Fever and Neutropenia Guidelines (IPFNG) indicate that the addition of empiric antifungal therapy may be warranted for high-risk patients who have persistent fever after four to seven days of broad-spectrum antibiotics and no identified source of fever

Antifungal therapy

- Before initiating antifungal therapy, *suggested evaluations include abdominal imaging, computed tomography (CT) of the chest, CT of the sinuses* (in patients with localizing signs or symptoms), and biopsy of any suspicious lesions .
- The 2017 IPFNG suggest that galactomannan should not be used to guide initiation of empiric antifungal therapy because of its poor positive predictive value and inability to exclude non-*Aspergillus* molds .
- Although beta-D glucan is widely used in adult cancer patients, it is not recommended in children because its diagnostic accuracy has not been demonstrated in this population .

Antifungal therapy

- Empiric antifungal therapy is usually continued until resolution of neutropenia in the absence of evidence of invasive fungal infection .
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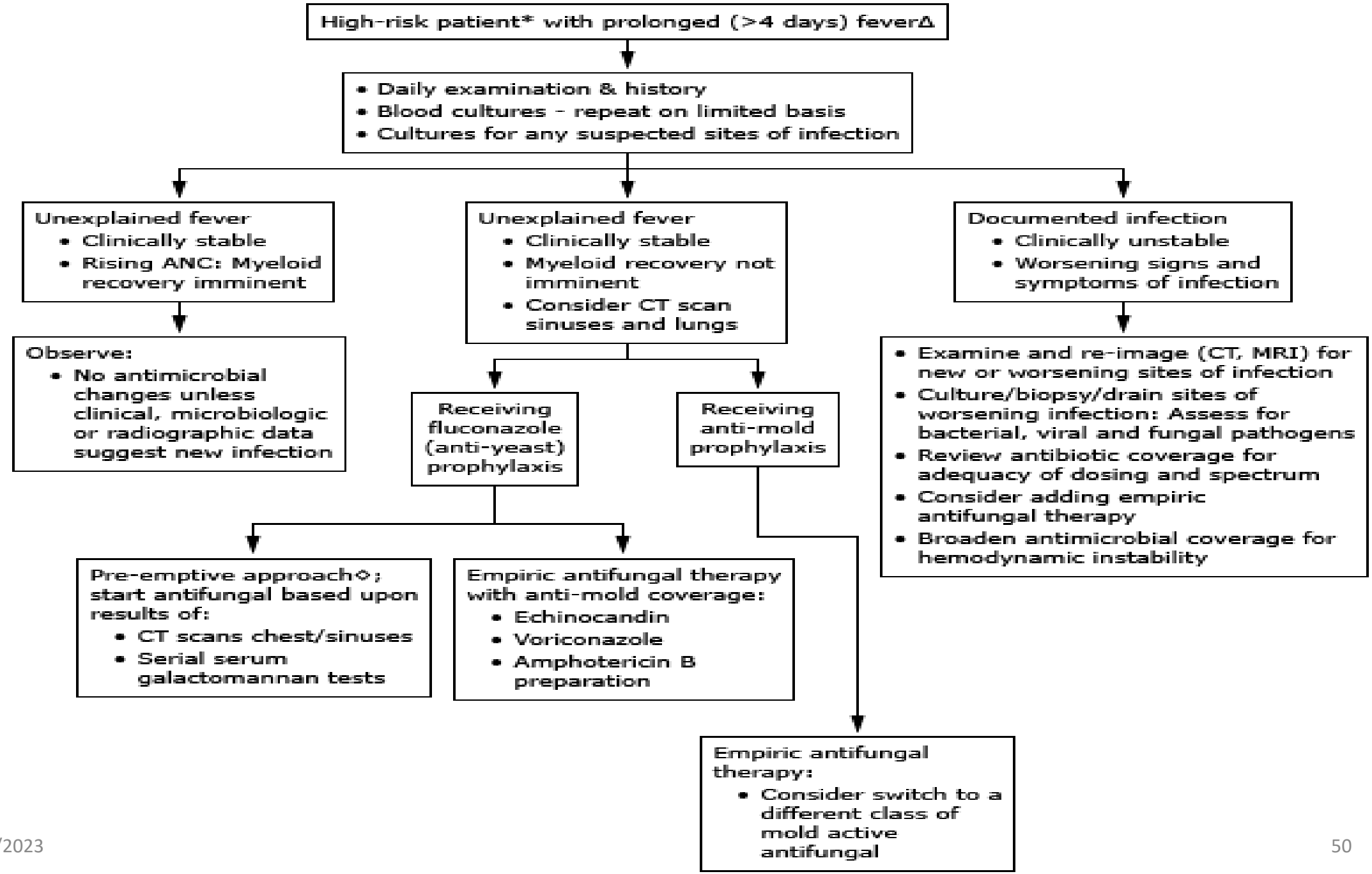
High-risk patient* with prolonged (>4 days) feverΔ
• Daily examination & history
• Blood cultures – repeat on limited basis
• Cultures for any suspected sites of infection
Unexplained fever
• Clinically stable
• Rising ANC: Myeloid recovery imminent
Observe:
• No antimicrobial changes unless clinical, microbiologic or radiographic data suggest new infection
Unexplained fever
• Clinically stable
• Myeloid recovery not imminent
• Consider CT scan sinuses and lungs
Receiving fluconazole (anti-yeast) prophylaxis
Receiving anti-mold prophylaxis
Pre-emptive approach◇; start antifungal based upon results of:
• CT scans chest/sinuses
• Serial serum galactomannan tests
Empiric antifungal therapy with anti-mold coverage:
• Echinocandin
• Voriconazole
• Amphotericin B preparation
Empiric antifungal therapy:
• Consider switch to a different class of mold active antifungal
Documented infection
• Clinically unstable
• Worsening signs and symptoms of infection
• Examine and re-image (CT, MRI) for new or worsening sites of infection
• Culture/biopsy/drain sites of worsening infection: Assess for bacterial, viral and fungal pathogens
• Review antibiotic coverage for adequacy of dosing and spectrum
• Consider adding empiric antifungal therapy
• Broaden antimicrobial coverage for hemodynamic instability

Duration of therapy

- — The duration of empiric antibiotic therapy depends upon the clinical circumstances of the individual patient.
- ***The traditional endpoint has been*** *negative blood cultures for at least 48 hours,* ***resolution*** *of fever for at least 24 hours,* ***and resolution of neutropenia (ie,*** *[ANC] >500* ***cells/microL) .***

Duration of therapy

- Data from a small retrospective study suggest that patients who are afebrile for at least 24 hours, are in good clinical condition, have been treated with intravenous antibiotics for a minimum of 72 hours, and have no identified infectious source can be discharged from the hospital without antibiotics before evidence of marrow recovery .


Thanks