Therapy of Infections in Neutropenic Patients

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Introduction

An immunocompromised host is a patient with defects in host defenses that predispose to infection.

Risk factors include:

1. **Neutropenia.**
2. **Immune system defects (from disease or immunosuppressive drug therapy).**
3. **Compromise of natural host defenses.**
4. **Environmental contamination.**
5. **Changes in the normal flora of the host.**

Risk Factors for Infection

1. Neutropenia:

- **Neutropenia is defined as an abnormally reduced number of neutrophils circulating in peripheral blood.**
- **An absolute neutrophil count (ANC) of less than 1,000 cells/mm^3 indicates a reduction sufficient to predispose patients to infection.**

Risk Factors for Infection

The development of infection depends on:

a) **the severity of neutropenia**
b) **the rate of neutrophil decline**
c) **the duration of neutropenia**

Risk Factors for Infection

- **All neutropenic patients are considered to be at risk for infection, but those with ANC less than 500 cells/mm^3 are at greater risk than those with ANCs of 500 - 1,000 cells/mm^3.**
- **Bacteria and fungi commonly cause infections in neutropenic patients.**

Risk Factors for Infection

2. Immune System Defects:

- **Defects in T-lymphocyte and macrophage function (cell-mediated immunity), B-cell function (humoral immunity), or both predispose patients to infection.**

Risk Factors for Infection

3. Destruction of Protective Barriers:

- **This is a major factor predisposing immunocompromised patients to infection.**

a) **Damage to skin and mucous membranes by surgery, venipuncture, IV and urinary catheters, radiation, and chemotherapy.**

b) **Chemotherapy-induced mucositis of the oropharynx and GIT establish a portal for subsequent infection by bacteria, HSV, and *Candida*.**

Risk Factors for Infection

c) **Medical and surgical procedures, such as transplant surgery, indwelling IV catheter placement, bone marrow aspiration, biopsies, and endoscopy, further damage the skin & mucous membranes and predispose patients to infection.**

- **Infections resulting from disruption of protective barriers usually are caused by skin flora such as *S. aureus*, *S. epidermidis*, and various streptococci.**

Risk Factors for Infection

4. **Environmental contamination:**

a) **Contaminated equipment such as nebulizers and ventilators, and contaminated water supplies predispose for outbreaks of *P. aeruginosa* and *Legionella pneumophila* infections, respectively.**

b) **Fruits and green leafy vegetables are sources of gram negative bacteria and fungal infections in immunocompromised hosts.**

Risk Factors for Infection

5. **Changes in the normal microbial flora of the host:**

a) **Administration of broad-spectrum antimicrobial agents disrupts GIT flora and predisposes patients to infection with more virulent pathogens.**

b) **Antineoplastic drugs (cyclophosphamide, doxorubicin, and fluorouracil, …) and acid-suppressive therapy (histamine H_2-receptor antagonists, proton-pump inhibitors, and antacids) also may disrupt GIT flora and predispose to infection.**

Risk Factors and Common Pathogens in Immunocompromised Patients

Risk Factor	Patient Condition	Common Pathogens
Neutropenia	Acute leukemia Chemotherapy	Bacteria: Staphylococcus aureus, Staphylococcus epidermidis, and other coagulase-negative staphylococci, streptococci, enterococci are most common, followed by Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Fungi: Candida, Aspergillus, Mucorales (Mucor) Viruses: Herpes simplex
Impaired cell-mediated immunity	Lymphoma Immunosuppressive therapy (steroids, cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine and anti-neoplastic agents	Bacteria: Listeria, Nocardia, Legionella, Mycobacteria Fungi: Cryptococcus neoformans, Candida, Aspergillus, Histoplasma capsulatum Viruses: Cytomegalovirus, varicella-zoster, herpes simplex Pneumocystis jiroveci **Yeast-like fungus**
Impaired humoral immunity	Multiple myeloma, Chronic lymphocytic leukemia (have progressive hypogammaglobulinemia) Splenectomy Immunosuppressive therapy (steroids, chemotherapy)	Bacteria: encapsulated organisms such as S. pneumoniae, H. influenzae, N. meningitidis Which might produce life-threatening infections

Loss of protective skin barriers	Venipuncture, bone marrow aspiration, urinary catheterization, vascular access devices, radiation, biopsies	Bacteria: S. aureus, S. epidermidis, Bacillus spp., Corynebacterium jeikeium Fungi: Candida
Loss of protective mucous membranes barriers	Respiratory support equipment, endoscopy, chemotherapy, radiation	Bacteria: S. aureus, S. epidermidis, streptococci, Enterobacteriaceae, P. aeruginosa, Bacteroides spp. Fungi: Candida Viruses: Herpes simplex
Surgery	Solid-organ transplantation	Bacteria: S. aureus, S. epidermidis, Enterobacteriaceae, P. aeruginosa, Bacteroides spp. Fungi: Candida Viruses: Herpes simplex
Alteration of normal microbial flora	Antimicrobial therapy Chemotherapy Acid –lowering agents Hospital environment	Bacteria: Enterobacteriaceae, P. aeruginosa, Legionella, S. aureus, S. epidermidis Fungi: Candida, Aspergillus
Blood products, donor organs	Bone marrow transplantation Solid-organ transplantation	Fungi: Candida Viruses: Cytomegalovirus, Epstein–Barr virus, hepatitis B, hepatitis C Protozoa: Toxoplasma gondii

Management of Febrile Episodes in Neutropenic Patients

Goals of therapy:

1. **Protect the patient from early death caused by undiagnosed infection.**
2. **Prevent breakthrough bacterial, fungal and viral infections during periods of neutropenia.**
3. **Effectively treat established infections.**
4. **Reduce morbidity.**

Management of Febrile Episodes in Neutropenic Patients

5. **Avoid unnecessary use of antimicrobials that contribute to increased resistance.**
6. **Minimize toxicities and cost of antimicrobial therapy while increasing patient quality of life.**

- **Empirical broad-spectrum antibiotic therapy is effective at reducing early mortality.**

Management of Febrile Episodes in Neutropenic Patients

Approach to Treatment:

- **Both treatment and prophylaxis of infectious complications, can be extremely challenging.**
- **Although published guidelines are available, the most optimal clinical management of these patients remains unclear in many aspects.**
- **Fever in the neutropenic patient should be considered to be due to infection until proven otherwise.**

Management of Febrile Episodes in Neutropenic Patients

1. High-dose broad-spectrum bactericidal, parenteral, empirical antibiotic therapy should be initiated at the onset of fever or at the first signs or symptoms of infection.

a) Withholding antibiotic therapy until an organism is isolated results in unacceptably high mortality rates.

Management of Febrile Episodes in Neutropenic Patients

b) Undiagnosed infection in immunocompromised patients can rapidly disseminate and results in death.

c) Empirical antibiotic therapy is 70-90% effective at reducing early morbidity and mortality.

2. Antimicrobial therapy must be appropriate and should be initiated promptly in afebrile patients with clinical signs and symptoms of infection.

Management of Febrile Episodes in Neutropenic Patients

3. When designing optimal empirical antibiotic regimens, physicians must consider infection patterns and antimicrobial susceptibility trends in their respective institutions.
4. Patient factors such as, risk of infection, drug allergies, concomitant nephrotoxins, and previous antimicrobial exposure (including prophylaxis) must be considered.

Management of Febrile Episodes in Neutropenic Patients

5. **Risk stratification drives both type and setting of antimicrobial therapy:**

1) **Low-risk patients:**

a) **have an anticipated duration of neutropenia ≤ 7 days.**

b) **are clinically stable.**

c) **have no or few co-morbidities.**

d) **have no bacterial focus or systemic signs of infection other than fever.**

Management of Febrile Episodes in Neutropenic Patients

2) **High-risk patients:**

a) are those with an anticipated duration of neutropenia of > 7 days

b) have profound neutropenia

c) are clinically unstable

d) have comorbid medical problems (focal or systemic signs of infection, GI symptoms, nausea, vomiting, diarrhea, hypoxemia, and chronic lung disease), or have a high-risk cancer (acute leukemia) and/or have undergone high intensity chemotherapy.

Management of Febrile Episodes in Neutropenic Patients

- **High-risk patients should be hospitalized for parenteral antibiotics, whereas low-risk patients may be candidates for oral or outpatient antibiotics.**
- **Because of their frequency and relative pathogenicity, *P. aeruginosa* and other gram-negative bacilli and *staphylococci* are the primary targets of empirical antimicrobial therapy.**

Management of Febrile Episodes in Neutropenic Patients

- **The optimal antibiotic regimen remains controversial.**
- **All empirical regimens must be: carefully monitored and appropriately revised on the basis of documented infections, susceptibilities of bacterial isolates, development of more defined clinical signs and symptoms of infection, or a combination of these factors.**

Management of Febrile Episodes in Neutropenic Patients

Recognized antibiotic regimens:

1. **Monotherapy with an antipseudomonal β-lactam (cefepime or ceftazidime), a carbapenem (imipenem–cilastatin or meropenem), or piperacillin–tazobactam.**
2. **Two-drug combination therapy with an antipseudomonal β-lactam + either an aminoglycoside or an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin).**
3. **Monotherapy or two-drug combination therapy as above, + the addition of vancomycin.**

Management of Febrile Episodes in Neutropenic Patients

- **There is no significant difference, overall, between monotherapy and combination therapy (β-lactam/aminoglycoside) in rates of survival, response, and bacterial/fungal superinfections.**

Management of Febrile Episodes in Neutropenic Patients

- **A higher rate of adverse effects was observed in aminoglycoside-containing combination regimens.**
- **Cefepime and antipseudomonal carbapenems have good activity against viridans streptococci and pneumococci but not all gram positive bacteria.**

Management of Febrile Episodes in Neutropenic Patients

Disadvantages:

Regimen 1:

limited gram positive activity, and high rate of superinfection).

Regimen 2:

1. **Antipseudomonal β-lactam + aminoglycoside: limited gram positive activity, potential for nephrotoxicity and need of TDM.**
2. **Antipseudomonal β-lactam + fluoroquinolone: limited gram positive activity and development of resistance.**

Regimen 3:

Selection of vancomycin resistant enterococci, risk of nephrotoxicity and need for TDM.

Management of Febrile Episodes in Neutropenic Patients

Oral antibiotic regimen for low risk patients:

Ciprofloxacin or levofloxacin + amoxicillin-clavulanate or clindamycin.

Disadvantages:

1) **Least studied.**
2) **Requires compliant patients with 24-hour access to medical care in case it is needed.**
3) **Requires supporting home environment.**

Antimicrobial Therapy After Initiation of Empirical Therapy

- After 2 to 4 days of empirical antimicrobial therapy, the clinical status and culture results should be reevaluated to determine whether therapeutic modifications are necessary.
- During periods of neutropenia, patients should continue to receive broad-spectrum therapy because of risk of secondary infections or breakthrough bacteremia when antimicrobial coverage is too narrow.

Antimicrobial Therapy After Initiation of Empirical Therapy

- **Duration of treatment should be appropriate for the particular organism and site, and should continue for at least the duration of neutropenia (until ANC ≥ 500 cells/mm^3) or longer if clinically necessary.**
- **In patients who become afebrile after 2 to 4 days of therapy with NO infection identified, continue antibiotic therapy until neutropenia has resolved (ANC ≥ 500 cells/mm^3).**

Antimicrobial Therapy After Initiation of Empirical Therapy

- **You may switch therapy to an oral regimen (ciprofloxacin plus amoxicillin–clavulanate) after 2 days of IV therapy, in low-risk patients who become afebrile and who have NO evidence of infection.**
- **In high-risk patients, parenteral antibiotic regimens should be continued until resolution of neutropenia.**

Antimicrobial Therapy After Initiation of Empirical Therapy

Fever after 2 or more days of antibiotic therapy can be due to:

1) nonbacterial infection
2) resistant bacterial infection or infection slow to respond to therapy
3) emergence of a secondary infection
4) inadequate drug concentrations
5) drug fever
6) infection at a non-vascular site (catheter infection or abscess)
7) noninfectious causes such as:

a. tumors
b. administration of blood products

Antimicrobial Therapy After Initiation of Empirical Therapy

- **Persistently febrile patients should be evaluated carefully, but modifications generally are NOT made to initial antimicrobial regimens within the first 2 to 4 days of therapy unless there is evidence of clinical deterioration.**

Antimicrobial Therapy After Initiation of Empirical Therapy

- Antibiotic regimens may require modification in patients experiencing toxicities as well as in patients with evidence of progressive disease, clinical instability, or documentation of an organism NOT covered by the initial regimen.

Antimicrobial Therapy After Initiation of Empirical Therapy

- **Addition of vancomycin should be considered, if NOT already part of the regimen.**
- **If vancomycin was included in the initial empirical regimen and the patient is still febrile after 2 to 3 days of therapy without isolating a gram-positive pathogen, discontinuation of vancomycin should be considered to reduce the risk of toxicities or resistance.**

Initiation of Antifungal Therapy

- **Neutropenic patients who remain febrile despite > 4 - 7 days of broad-spectrum antibiotic therapy are candidates for antifungal therapy.**
- **A significant percentage of febrile patients who die during prolonged neutropenia have evidence of invasive fungal infection on autopsy, even when they have NO evidence of fungal disease before death.**

Initiation of Antifungal Therapy

- **Persistence of fever or development of a new fever during broad-spectrum antibiotic therapy may indicate the presence of a fungal infection, most commonly *Candida* or *Aspergillus* spp.**
- **Blood cultures for fungi are positive in < 50% of neutropenic patients with invasive fungal infections, and waiting for isolation of fungal organisms is associated with high morbidity and mortality.**

Initiation of Antifungal Therapy

- **Empirical antifungal therapy, thus, should be initiated after 4 to 7 days of broad-spectrum antibiotic therapy in persistently febrile patients if the duration of neutropenia is expected to be greater than 1 week.**
- **Antifungal therapy must be adequate to treat undiagnosed fungal infection and prevent fungal superinfection in high-risk patients.**

Initiation of Antifungal Therapy

- **Empirical coverage for both *Candida* spp. and *Aspergillus* should be considered because these organisms are responsible for more than 90% of fungal infections in neutropenic patients.**

Initiation of Antifungal Therapy

- *Aspergillus* is particularly common in patients with hematologic malignancies and amphotericin B is the preferred agent.
- Lipid-associated amphotericin B (LAMB) products are similar in efficacy to conventional amphotericin B while causing fewer toxicities, and can be used at higher doses (3 mg/kg).
- LAMB products have significantly higher cost.

Initiation of Antifungal Therapy

- **The azole compounds are associated with emergence of resistant *Candida* strains.**
- **Fluconazole has good activity against *C. albicans* but lacks activity against *Aspergillus*.**
- **Voriconazole is a preferred agent for invasive aspergillosis (especially pulmonary) due to improved survival and less toxicity when compared to amphotericin B.**

Initiation of Antifungal Therapy

- **Posaconazole has extended activity against some *Mucorales,* in addition to *Candida* and *Aspergillus*, but is only approved for prophylaxis of *Aspergillus* and *Candidal* infections in neutropenic patients.**
- **TDM is recommended for some azole antifungals given the potential for interpatient variability, therapeutic failure associated with subtherapeutic concentrations, and toxicities associated with supratherapeutic concentrations.**

Initiation of Antifungal Therapy

- **The echinocandin antifungals (caspofungin, micafungin, and anidulafungin) have broad spectrum of antifungal activity and favorable adverse effect profiles.**
- **Caspofungin is as effective as, and better tolerated than, liposomal amphotericin B for empirical treatment of neutropenic patients with persistent fever. Therefore, it is considered an appropriate alternative to LAMB and voriconazole.**

Monitoring of Antifungal Agents

Drug	Adverse Reaction	Monitoring Parameters	Comments
Amphotericin B (lipid-associated)	Nephrotoxicity, hepatotoxicity, electrolyte disturbances, infusion reactions	Serum creatinine, electrolytes, LFTs, blood pressure, heart rate	Liposomal preparations associated with less renal toxicity, similar efficacy to standard preparation. Electrolyte disturbances occur before creatinine alterations. Pretreatment and slow infusion may decrease incidence of infusion reaction

Posaconazole	**Hepatotoxicity, rash; interactions with CYP3A4**	**LFTs, skin, posaconazole serum concentrations**	**Poor absorption with suspension, goals of >1 µg/mL for treatment and >0.7 µg /mL for prophylaxis. Parenteral formulation not recommended for patients with CrCL <50 mL/min. Multiple interactions with drugs metabolized by CYP 3A4, including immunosuppressants; close monitoring needed.**
Voriconazole	**Mental status changes, headache, hallucinations, visual disturbances, hepatotoxicity, QTc prolongation; interactions with CYPs 2C9, 2C19, and 3A4**	**Mental status, visual function, LFTs, ECG, voriconazole serum concentrations**	**Mental status/visual changes associated with elevated troughs > 5.5 µg /m; goal trough 1-5.5 µg/mL for treatment and prophylaxis, target trough of > 2 µg/ml in disease with poor prognosis. Parenteral formulation not recommended for patients with CrCL<50 mL/min. Multiple interactions**

Initiation of Antiviral Therapy

- **Febrile neutropenic patients with vesicular or ulcerative skin or mucosal lesions should be evaluated carefully for infection due to herpes simplex virus (HSV) or varicella-zoster virus (VZV).**
- **Mucosal lesions from viral infections provide a portal of entry for bacteria and fungi during periods of immunosuppression.**

Initiation of Antiviral Therapy

- **If viral infection is presumed or documented, neutropenic patients should receive aggressive antiviral therapy to aid healing of primary lesions and prevent disseminated disease.**

Initiation of Antiviral Therapy

- **Acyclovir and the newer antivirals valacyclovir and famciclovir may be used.**
- **Routine use of antiviral agents in the management of patients without mucosal lesions or other evidence of viral infection is NOT recommended.**

Initiation of Antiviral Therapy

Adverse reactions of acyclovir:

Nausea, diarrhea, headache
IV administration may be associated with reversible crystalline nephropathy or interstitial nephritis; or neurologic toxicity (tremors, delirium, seizures).
These are uncommon with adequate hydration and avoidance of rapid infusion rates.
Drug Interactions:
Probenecid and cimetidine decrease acyclovir clearnce and increase exposure.
Acyclovir + zidovudine → somnolence and lethargy.

Duration of Antimicrobial Therapy

- **The optimal duration of antimicrobial therapy remains controversial.**
- **Decisions regarding discontinuation of empirical antimicrobial therapy are more difficult than those of initiation of therapy.**
- **The patient's ANC is the most important factor for the total duration of antibiotic therapy:**

Duration of Antimicrobial Therapy

- **If ANC is ≥ 500 cells/mm^3 for two consecutive days, if the patient is afebrile and clinically stable for 48 hours or more, and if NO pathogen has been isolated, antibiotics may be discontinued.**
- **Some clinicians advocate that patients with ANC < 500 cells/mm^3 be maintained on antibiotic therapy until resolution of neutropenia, even if they are afebrile.**

Duration of Antimicrobial Therapy

- **Prolonged antibiotic use has been associated with superinfections resulting from resistant bacteria and fungi and increased risk of antibiotic-related toxicities.**
- **If low-risk patients are stable clinically with negative cultures but the ANC still is < 500 cells/mm^3) antibiotics may be discontinued after a total of 5 - 7 afebrile days.**

Duration of Antimicrobial Therapy

- **Patients with severe neutropenia (ANC > 100 but < 500 cells/mm^3), mucosal lesions, or unstable vital signs or other risk factors should continue to receive antibiotics until ANC becomes ≥ 500 cells/mm^3, and the patient is stable clinically.**

Duration of Antimicrobial Therapy

- **Patients with documented infections should receive antimicrobial therapy until the infecting organism is eradicated and signs and symptoms of infection have resolved (at least 10-14 days of therapy).**
- **Any way, therapy must be individualized based on individual patient parameters and response to therapy.**

Colony-Stimulating Factors (CSFs)

Granulocyte-macrophage colony-stimulating Factor (Sargramostim)

Granulocyte colony-stimulating factor (filgrastim)

- **May be used as adjunct therapy to antimicrobial treatment of febrile neutropenic patients.**

1. **They reduce total duration and severity of chemotherapy-related neutropenia.**
2. **They reduce duration of antibiotic use.**
3. **They reduce hospitalizations, and decrease hospital length of stay.**
4. **Overall mortality or infection-related mortality is NOT decreased.**

Colony-Stimulating Factors (CSFs)

- **CSFs should NOT be routinely used in patients with uncomplicated fever and neutropenia.**
- **Patients with prolonged neutropenia and documented severe infections who are NOT responding to appropriate antimicrobial therapy may benefit from treatment with CSFs.**
- **CSFs should be considered in patients who are at high risk of infection-associated complications, or who have factors that are predictive of poor clinical outcomes:**

Colony-Stimulating Factors (CSFs)

1) Profound neutropenia (ANC <100 cells/mm^3)
2) Expected prolonged period of neutropenia (>10 days)
3) Patient age >65 years
4) Uncontrolled primary disease
5) Sepsis syndrome, or severe infection manifest by hypotension and multiorgan dysfunction
6) Pneumonia
7) Invasive fungal infection
8) Other clinically documented infection
9) Hospitalized at the time of the development of fever
10) Severe complications during previous episode of febrile neutropenia.

Colony-Stimulating Factors (CSFs)

Granulocyte CSF (or GM-CSF) Common Adverse Effects:

1. Bone pain: because of proliferation of WBCs in bone marrow. Relieved with analgesics.
2. Leukocytosis.
3. Bruises, bleeding gum and nose bleeding: Due to drop in platelet count.
4. Headache
5. Fatigue: can be prolonged up to one year.
6. Back pain.
7. Hepatic problems: reversible with discontinuation of the drug
8. Diarrhea or constipation.

Colony-Stimulating Factors (CSFs)

9. Malaise.
10. Fever
11. Splenomegally
12. Splenic rupture is a rare but serious.
13. Inflammation around the injection site.
14. Abdominal pain
15. Edema in hands and feet, peripheral edema and pleural or pericardial effusions due to a capillary leak syndrome.
16. Insomnia.
17. Arthralgias & myalgias.