Therapy of Infections in Neutropenic Patients

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.**
- **The severity of neutropenia, the rate of neutrophil decline, and the duration of neutropenia are important risk factors for infection.**

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.**
- **Damage to skin and mucous membranes by surgery, venipuncture, IV and urinary catheters, radiation, and chemotherapy, disrupts natural host defense systems, with high risk for infection.**
- **Chemotherapy-induced mucositis of the oropharynx and GIT establish a portal for subsequent infection by bacteria, HSV, and *Candida*.**

Risk Factors for Infection

- **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/Alteration of Microbial Flora:**

- **Infections in immunocompromised patients are caused by organisms either colonizing the host or acquired from the environment.**
- **Microorganisms may be transferred easily from patient to patient on the hands of hospital personnel unless strict infection control guidelines are followed.**

Risk Factors for Infection

- **Contaminated equipment, such as nebulizers or ventilators, and contaminated water supplies have been responsible for outbreaks of *P. aeruginosa* and *Legionella pneumophila* infections, respectively.**
- **Foods, such as fruits and green leafy vegetables, which often are colonized with gram-negative bacteria and fungi, are sources of microbial contamination in immunocompromised hosts.**

Risk Factors for Infection

- **Administration of broad-spectrum antimicrobial agents disrupts GIT flora and predisposes patients to infection with more virulent pathogens.**
- **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 possibly predispose patients 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 Protozoa: Pneumocystis jiroveci
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, viral, and protozoal 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:

1. **Both treatment and prophylaxis of infectious complications, can be extremely challenging.**
2. **Although published guidelines are available, the most optimal clinical management of these patients remains unclear in many aspects.**

Management of Febrile Episodes in Neutropenic Patients

3. Fever in the neutropenic patient should be considered to be due to infection until proven otherwise.
4. 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.
5. Withholding antibiotic therapy until an organism is isolated results in unacceptably high mortality rates.

Management of Febrile Episodes in Neutropenic Patients

- **Undiagnosed infection in immunocompromised patients can rapidly disseminate and results in death.**
- **Empirical antibiotic therapy is 70-90% effective at reducing early morbidity and mortality.**

6. **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

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

Management of Febrile Episodes in Neutropenic Patients

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

a) **Low-risk patients have: an anticipated duration of neutropenia ≤ 7 days, are clinically stable, have no or few co-morbidities, and no bacterial focus or systemic signs of infection other than fever.**

Management of Febrile Episodes in Neutropenic Patients

b) High-risk patients are those: with an anticipated duration of neutropenia of > 7 days, profound neutropenia, are clinically unstable or 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.**
- **The optimal antibiotic regimen for empirical therapy in febrile neutropenic patients remains controversial, but it is clear that no single regimen can be recommended for all patients.**

Management of Febrile Episodes in Neutropenic Patients

- **Because of their frequency and relative pathogenicity, *P. aeruginosa* and other gram-negative bacilli and *staphylococci* are the primary targets of empirical antimicrobial therapy.**
- **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 differences, overall, between monotherapy and combination therapy (β-lactam/aminoglycoside) in rates of survival, response, and bacterial/fungal superinfections.**
- **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.**

Comparative Advantages and Disadvantages of Various Antibiotic Regimens for Empiric Therapy of Febrile Neutropenic Patients

Regimen	Potential Advantages	Potential Disadvantages
β-Lactam monotherapy (ceftazidime, cefepime, piperacillin–azobactam, imipenem–cilastatin, or meropenem)	Efficacy comparable to combination regimens; decreased drug toxicities; ease of administration; possibly lessexpensive	Possibly less efficacy in profound neutropenia or prolonged neutropenia; limited gram-positive activity; no potential for additive/synergistic effects; increased selection of resistant organisms; increased colonization and superinfection rates

Antipseudomonal β-lactam plus aminoglycoside (eg, gentamicin or tobramycin + cefepime, ceftazidime, or piperacillin– tazobactam)	Traditional regimen, broadspectrum coverage; optimal therapy of Pseudomonas aeruginosa; rapidly bactericidal; synergistic activity; decreased bacterial resistance; reduction of superinfections	Limited gram-positive activity; potential for nephrotoxicity; need for therapeutic monitoring of aminoglycoside concentrations
Antipseudomonal β-lactam plus fluoroquinolone (ciprofloxacin or higher-dose levofloxacin + ceftazidime, cefepime, or piperacillin–tazobactam)	Efficacy similar to other regimens when used in combination therapy; no cross-resistance with β-lactams; possibility for oral administration; may be useful in patients with renal impairment in whom aminoglycosides are undesirable	Marginal gram-positive activity; fluoroquinolones not recommended as monotherapy; resistance may develop rapidly

Empirical regimens containing vancomycin (added to antipseudomonal β-lactam ± aminoglycoside or fluoroquinolone)	Early effective therapy of gram-positive infections	No demonstrated benefit of vancomycin empirical therapy versus addition of vancomycin if needed later; increased risk of selection for vancomycin-resistant enterococci; risk of toxicities; excessive cost; need for therapeutic monitoring of vancomycin concentrations
Oral antibiotic regimens (ciprofloxacin or levofloxacin + amoxicillin–clavulanate or clindamycin)	Efficacy comparable with parenteral therapy in low-risk patients; less expensive; reduced exposure of patients to nosocomial pathogens	Least studied treatment approach; less potent than parenteral antibiotics; requires compliant patient with 24-hour access to medical care should clinical instability develop

Antimicrobial Therapy After Initiation of Empirical Therapy

- **After 2 to 4 days of empirical antimicrobial therapy, the clinical status and culture results of febrile neutropenic patients 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.
- 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 to 7 days of broad-spectrum antibiotic therapy are candidates for antifungal therapy.**
- **A high percentage of febrile patients who die during prolonged neutropenia have evidence of invasive fungal infection on autopsy, even when they nave 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 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. Dose (3 mg/kg).
- LAMB products have significantly higher cost.

Initiation of Antifungal Therapy

- **The azole compounds are associated with emergence of *Candida* strains resistant to them.**
- **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 fungal 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.**

Pathogen	Syndrome	Recommended Treatment
Candida spp.	Blood, urinary tract, mucous membranes, skin, disseminated disease	Clotrimazole; nystatin; fluconazole; itraconazole; amphotericin B ± 5-flucytosine; lipid-associated amphotericin B (LAMB); caspofungin; micafungin; anidulafungin
Aspergillus spp.	Skin, pulmonary, CNS	Voriconazole; LAMB; caspofungin; micafungin; posaconazole; itraconazole
Cryptococcus neoformans	Skin, pulmonary, CNS	LAMB + 5-flucytosine; fluconazole
Mucorales (Mucor)	Rhinocerebral disease	LAMB; posaconazole

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 HSV or varicella-zoster virus (VZV).**
- **Mucosal lesions from viral infections provide a portal of entry for bacteria and fungi during periods of immunosuppression.**
- **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.**
- **Treatment recommendations for viral infections are as follows:**

Pathogen	Syndrome	Recommended Treatment
Herpes simplex virus	Skin, CNS, mucous membranes, pulmonary	Acyclovir; foscarnet
Human herpesvirus-6	CNS, hepatic, bone marrow	Ganciclovir; foscarnet
Cytomegalovirus	Pulmonary, blood, urinary tract, GI tract	Ganciclovir; foscarnet; immunoglobulin
Varicella-zoster virus	Skin, disseminated disease	Acyclovir; foscarnet
Epstein–Barr virus	Lymphoproliferative disease	Rituximab
Papovaviruses (BK, JC)	Skin, CNS	No effective treatment

Antiviral Drug	Adverse Reactions	Notes
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.	
Ganciclovir	Myelosuppression , Nausea and diarrhea Fever, rash, headache, Insomnia Peripheral neuropathy, CNS toxicity (confusion, seizures, psychosis), Hepatotoxicity May be carcinogenic, embryotoxic and may cause aspermatogenesis Levels increase in patients taking probenecid or trimethoprim	

Foscarnet	**Renal impairment. Prevented by saline preloading. More with other nephrotoxic drugs.** **Hypo- or hypercalcemia, Hypo- or hyperphosphatemia , Hypokalemia, Hypomagnesemia.** **Penile ulcerations, may be due to high level of ionized drug in urine.** **Nausea, vomiting.** **Anemia.** **Elevation of hepatic enzymes, and fatigue.** **CNS: headache, hallucinations, seizures.** **May cause chromosomal damage.**	
Rituximab	**Skin rash do not usually require discontinuation of therapy.** **Urticarial or anaphylactoid reaction precludes further therapy.** **Reduction in immunoglubulins.** **Rituximab has not been associated with either activation of tuberculosis or the occurrence of lymphomas or other tumors**	**(A chimeric monoclonal antibody against CD20)** **The mechanism of action includes complement-mediated lysis, antibody-dependent cellular cytotoxicity, and induction of apoptosis**

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, then antibiotics can 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 increases the 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 profound 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.**
- **Their use is associated with reduced total duration and severity of chemotherapy-related neutropenia, reduced duration of antibiotic use, fewer hospitalizations, and decreased hospital length of stay.**
- **Overall mortality or infection-related mortality is NOT decreased.**

Colony-Stimulating Factors (CSFs)

- **CSFs should NOT be routinely initiated 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 for 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.