



Management of Febrile Neutropenia in Patients with Hematological Malignancies: An Update

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I. Baseline Evaluation of Risk for Infection

The risk of infection in patients with hematological malignancies results from the sum of the interaction of three factors: host-related, environmental, and prophylaxis-related factors.

Depending on the sum of these interactions, patients can be stratified into 2 groups: high or low risk for infection (**Table 1**).

A. Host-related factors

1. *Net-state of immunosuppression.* Neutropenia (depth, duration, and pace) is one of the most important risk factors for infection. Other factors contributing to the immunosuppressive state include cellular dysfunction, humoral dysfunction, infection with immunomodulating viruses, malnutrition and older age, and concomitant immunosuppressive diseases (Table 1).^(1,2)

2. *Organ dysfunction.* The protective effect of the skin and mucous membrane is compromised by high doses of chemotherapy, irradiation, herpes virus infection, intravenous catheters, and in allogeneic stem cell transplant (SCT) recipients graft-versus-host disease (GVHD). Disruption of this barrier (mucositis) is prob-

ably the most important predisposing factor for infection by providing organisms with direct access to the bloodstream.⁽¹⁾

Other organ dysfunction known to predispose patients with hematological malignancies to serious infections include renal and liver failure (Table 1), obstruction of natural body passages, and asplenia (secondary to therapy, disease, or accident).

3. *Microbial colonization and reactivation of latent infection.* Colonizing microorganisms cause the overwhelming majority of infections in patients with hematological malignancies.⁽³⁾ Factors predisposing to colonization are the widespread use of broad-spectrum antimicrobial agents,⁽⁴⁾ prolonged hospitalization (especially in the intensive care unit), use of antacids,⁽⁵⁾ damage to the ciliary function, and presence of foreign bodies.

Latent infections, such as cytomegalovirus (CMV), Epstein-Barr virus, herpes simplex virus, hepatitis B virus or hepatitis C virus, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, may reactivate during immunosuppression.⁽⁶⁾

Table 1: Factors that increase the risk of infection among patients with hematological malignancies

Host-related	<ul style="list-style-type: none">• Older age (>40 years)• AML/AA, non-first remission malignancy• Immunomodulating viruses*• Organ dysfunction (including severe mucositis, renal failure, liver dysfunction, etc.)• Concomitant immunosuppressive diseases
Environment-related	<ul style="list-style-type: none">• Colonization with virulent pathogens (<i>Staphylococcus aureus</i>, <i>Pseudomonas aeruginosa</i>, <i>Candida</i> spp., moulds)• Heavy exposure to contaminated environment (water, food, inanimate objects, air)
Treatment-related	<ul style="list-style-type: none">• Prolonged neutropenia (>10 days)• CD4 cytopenia (<200 cells/ml)• Allogeneic BMT/ PBSCT if:<ol style="list-style-type: none">1. matched unrelated or mismatch related2. T-cell depleted3. GVHD II-IV4. standard conditioning regimen (as opposed to non-myeloablative conditioning regimens)• Autologous BMT/ PBSCT if: CD34⁺ infused (autologous) <2.0 x 10⁶/kg• Prior therapy with purine analogues and/or high-dose corticosteroids (>1 mg/kg/d for more than 2 weeks)

Abbreviations: AML, acute myeloblastic leukemia; AA, aplastic anemia; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; GVHD, graft vs. host disease

*Immunomodulating viruses: CMV, HIV, ? HHV-6, ? HHV-7

B. Environmental factors

Infections secondary to exposure to environmental factors can be either community or hospital acquired.

Examples of community-acquired pathogens include food, and water-borne pathogens (such as *Salmonella* spp., *Brucella melitensis*, *Listeria monocytogenes*, *Campylobacter jejuni*, *Cryptosporidium*) and organisms transmitted by exposure from infected individuals (e.g. respiratory viruses).

Hospital acquired infections can result from contact with a contaminated environment or contaminated personnel:

a) Contaminated environment: air (*Aspergillus*, herpes zoster virus, others), food (bacteria, fungi, and parasites), water (*Aspergillus*, *Fusarium*, *Legionella* spp., and certain gram-negative bacilli), or inanimate objects (such as vancomycin-resistant enterococci [VRE], *Clostridium difficile*).

b) Contaminated health care providers: VRE, methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, and *Candida* spp. infections.

C. Prophylaxis-related factors

The widespread use of prophylactic antimicrobial drugs has led to a change in the usual distribution of infections in patients with hematological malignancies:

1. A shift from infections by gram-negative organisms to infections by gram-positive organisms including a-hemolytic *Streptococci*, coagulase-negative *Staphylococci*, *Staphylococcus aureus*, and *Enterococci*.⁽²⁾ This change occurred primarily because of the increasing use of fluoroquinolone prophylaxis.
2. A shift from infections by *C. albicans* to infections by fluconazole-resistant *Candida* spp. (*C. glabrata*, and *C. krusei*) as a result of the widespread use of fluconazole prophylaxis.⁽⁷⁾
3. A reduction in the early incidence of CMV infection, yet with a concomitant increase of late-onset CMV disease in association with ganciclovir prophylaxis.⁽⁸⁾
4. An increasing incidence of opportunistic moulds (such as *Aspergillus* and *Fusarium*) in association with the administration of broad-spectrum antibiotics.^(9,10)

II. Clinical Evaluation of Febrile Neutropenia

The initial evaluation should focus on determining the potential site(s) of infection, the causative organisms, and assessing the patient's risk of developing complications.

A. History and physical examination

The evaluation of the medical history needs to address the patient's exposure to infectious diseases, e.g. transfusions, hepatitis, toxoplasmosis, tuberculosis and other infections, as well as the vaccination and dental history.

Aspects of the social history that relate to possible sources of infection, including sexual and contraceptive history, recreational drug use, travel and pet ownership, are also important clues. The most important component of the evaluation is the assessment of the type and intensity of previous immunosuppressive therapy and the character of the immunosuppression, e.g. neutropenia, lymphopenia, CD4 count < 200 cell/ul, hypogammaglobulinemia, asplenia. This information will allow a more accurate determination of the patient's likely infection. For example, allogeneic SCT recipients from matched unrelated donor with GVHD have different risk than autologous SCT recipients. The former is likely to have severe mould infections (e.g. *Aspergillus*, *Fusarium*) and CMV disease, while these organisms are extremely unlikely to be diagnosed in the latter. Other important historical factors include the remission status of underlying cancer and previous complications of cancer therapy (febrile neutropenia, pneumonia of unknown origin, response to antifungal therapy, other documented infections, and antimicrobial susceptibility of each pathogen isolated and the treatment received). The presence of structural abnormalities (e.g. cardiac valvular abnormalities, prosthetic biomaterials, dialysis access fistulae, others) must be ascertained as well as the traditional review of systems (**Table 2**).

The physical examination must focus special attention to areas likely to be infected including the upper and lower respiratory tracts, the perioral and perirectal areas, skin, and site(s) of intravascular catheters and bone marrow biopsies, and dentition.

B. Laboratory evaluation

Initial laboratory evaluation includes a complete blood count with differential and platelets count, liver and renal function tests, oxygen saturation, urinalysis, cultures (blood, urine, and others as clinically indicated), and tissue sampling of suspected sites (bronchoalveolar lavage, lumbar puncture, etc).

Chest radiographs are usually obtained, although their yield in asymptomatic patients is very low. Computerized tomography (chest, sinuses, brain, abdomen) may play a more important role depending on the clinical setting. Magnetic resonance imaging may also be useful.

One additional test that may prove to be useful is C-reactive protein (CRP). An increase in the level of CRP has been shown to have a strong predictive value in patients with bacterial and fungal infections, either as a single measurement (>200 mg/l) or as part of a battery of tests (>50 mg/l increase over 24 h).⁽¹¹⁾

Recent additions to the diagnostic armamentarium are serology and polymerase chain reaction (PCR). The serologic diagnosis of *Aspergillus* infection has been improved with the introduction of a new enzyme-linked

Table 2. Site-specific infections in patients with febrile neutropenia.

Syndrome	Infectious causes	Non-infectious causes	Empirical therapy*
Mouth and esophagus	HSV, <i>Candida</i> spp. Rarely: bacteria (streptococci, anaerobes), CMV, moulds	Drug toxicity, GVHD, acid reflux, irradiation	Acyclovir and/or a triazole
Pharyngitis	Respiratory viruses, bacteria (streptococci, chlamydia, mycoplasma) Rarely: <i>Candida</i> spp., CMV, moulds (<i>Aspergillus</i> spp., zygomycetes)	Same as above	No standard empirical therapy
Laryngitis & Epiglottitis	Respiratory viruses, HSV, bacteria (streptococci, <i>H. influenza</i> , <i>B. catarrhalis</i>), <i>Candida</i> spp. Rarely: CMV, VZV, <i>Aspergillus</i> spp.	Same as above Same as above	No standard empirical therapy No standard empirical therapy
Tracheitis	HSV, bacteria (staphylococci, streptococci). Rarely: CMV, <i>Aspergillus</i> spp.	Same as above	No standard empirical therapy
Pulmonary infiltrates			
Localized	Bacteria (<i>Legionella</i> , others), moulds, Rarely: TB, atypical mycobacteria, HSV, respiratory viruses	Pulmonary embolism and hemorrhage, tumor	Antibacterials (to include legionella) Antifungal (amphotericin B)
Diffuse	Respiratory viruses, HSV, CMV, PCP, bacteria (<i>Legionella</i> , <i>Mycoplasma</i> , others) Rarely: cryptococcus, TB, atypical mycobacteria, VZV	Drug toxicity, pulmonary edema, radiation pneumonitis, alveolar hemorrhage, ARDS, hypersensitivity drug reaction, idiopathic interstitial pneumonitis, leukoagglutinin reaction, GVHD, EBV-associated lymphoma, pulmonary veno-occlusive disease, alveolar proteinosis, bronchiolitis obliterans	Antibacterials (to include TMP-SMX in certain settings)
Sinusitis	Bacteria, respiratory viruses, moulds Rarely: atypical mycobacteria, CMV	Tumor	Antibacterials Antifungal (amphotericin B)
Skin and soft tissue lesions	Bacteria, HSV, VZV, moulds, <i>Candida</i> spp. Rarely: CMV, HHV-6, atypical mycobacteria	Drug toxicity, tumor, GVHD	Acyclovir Antifungal (amphotericin B)
Bloodstream infections	Bacteria, <i>Candida</i> spp. Rarely: atypical mycobacteria, moulds		Antifungal (amphotericin B)
Catheter-site inflammation	Bacteria, <i>Candida</i> spp. Rarely: moulds, mycobacteria	Chemical phlebitis, venous thrombosis	D/C catheter when indicated Consider vancomycin
Gut inflammation and/or Typhlitis	Bacteria (<i>C. difficile</i> , anaerobes), CMV Rarely: <i>Candida</i> spp., adenovirus, rotavirus, enteroviruses, moulds	Drug toxicity, bleeding, infarction, GVHD, tumor	Antibacterial (particularly metronidazole) Consider enterococcal coverage Antifungal (azole or amphotericin B)
CNS symptoms			
Localized	Bacteria (<i>Listeria</i> , others), moulds <i>Candida</i> spp., toxoplasma, HSV	Cerebro-vascular accident, drug toxicity, tumor	Antibacterials Antifungal (amphotericin B) Acyclovir (high-dose)
Diffuse	Bacteria, <i>Candida</i> spp., cryptococcus Rarely: VZV, HHV-6, CMV	Drug toxicity	
Hepatitis	Hepatitis A, B & C, CMV Rarely: CDC, HHV-6	Drug toxicity, GVHD, VOD	No standard empirical therapy
Genito-urinary infections	Bacteria, <i>Candida</i> spp. Rarely: adenovirus, BK virus, CMV	Drug toxicity	Antibacterials
Bone marrow suppression	CMV, HHV-6, parvovirus	Drug toxicity, tumor, GVHD, graft failure	No standard empirical therapy

* Initiate empirical therapy, search for specific pathogens, and adjust therapy according to results
Abbreviations: HSV, herpes simplex virus; CMV, cytomegalovirus; H, hemophilus; B, *Branhamella*; PCP, *Pneumocystis carinii* pneumonia; TB, mycobacterium tuberculosis; VZV, varicella-zoster virus, GVHD, graft vs. host disease; TMP-SMX, trimethoprim-sulfamethoxazole; CNS, central nervous system; CDC, chronic disseminated candidiasis; EBV, Epstein-Barr virus; C, clostridium; VOD, venoocclusive disease; HHV, human herpes virus; HB & C, hepatitis B and C; IVIG, intravenous immunoglobulin

immunosorbent assay test to detect *Aspergillus* galactomannan in blood, and with a new PCR assay.⁽¹²⁾ The antigenemia assay and PCR for CMV have changed our approach to managing CMV infection in allogeneic SCT recipients.⁽⁸⁾

The diagnosis of pulmonary infection has also been recently improved by the availability of assays to detect respiratory syncytial virus (RSV) and Influenza antigen in nasopharyngeal secretions,⁽¹³⁾ *Histoplasma* and *Legionella* antigens in urine, and PCR test for the detection of *Pneumocystis carinii*, *Legionella*, *Chlamydia*, *Mycoplasma*, and various *Mycobacteria*.⁽¹⁴⁾

The evaluation of infections of the central nervous system should now routinely include a PCR test for HSV, enteroviruses, bacteria, *Mycobacterium tuberculosis*, and probably CMV, VZV, JC virus and *Toxoplasma* depending on the clinical setting.^(14,15)

Table 3. Factors associated with increasing risk of complications with febrile neutropenia.

Medical factors

Hemodynamic instability

- Decrease in blood pressure
- Increase in heart rate (>100 bpm)

Organ/metabolic dysfunction

- Respiratory failure (PO₂<60 Torr)
- Renal failure
- Liver failure
- Cardiac failure (and/or arrhythmias)
- Altered mental status and/or witnessed syncopal episode
- Profound weakness
- Severe hypercalcemia/hyperglycemia, and/or electrolytes imbalances
- Deep venous thrombosis
- Inadequate fluid intake

Hemostatic disorder

- Uncontrolled bleeding and/or severe thrombocytopenia (<10,000 platelets/mm³)

Serious infections

- Pneumonia
- Bacteremia
- Perirectal abscess
- Acute abdomen/ Typhlitis
- Meningitis

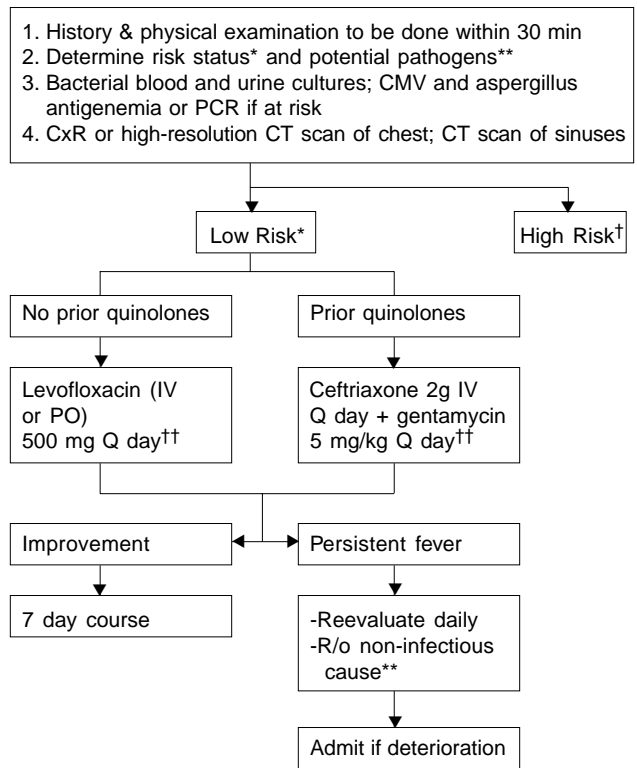
Cancer and its treatment

- Uncontrolled cancer
- High-dose chemotherapy likely to result in neutropenia (>10-14 days) and severe mucositis
- Allogeneic bone marrow transplantation

Socio-economic factors

- Inability to understand and use available emergency services
- >2h surface travel between the patient's home and hospital
- Lack of 24-hour companion at home
- Lack of availability of telephone communication

Abbreviations: PO₂: partial pressure of oxygen, bpm: beat per minute



* See Tables 1 & 3

** See Table 2

† See Figure 2

†† Antibacterials given as recommended regimen. Other choices available (Table 5)

Abbreviations: CMV: cytomegalovirus, PCR: polymerase chain reaction

Figure 1. Acute management of febrile neutropenia.⁽¹⁾

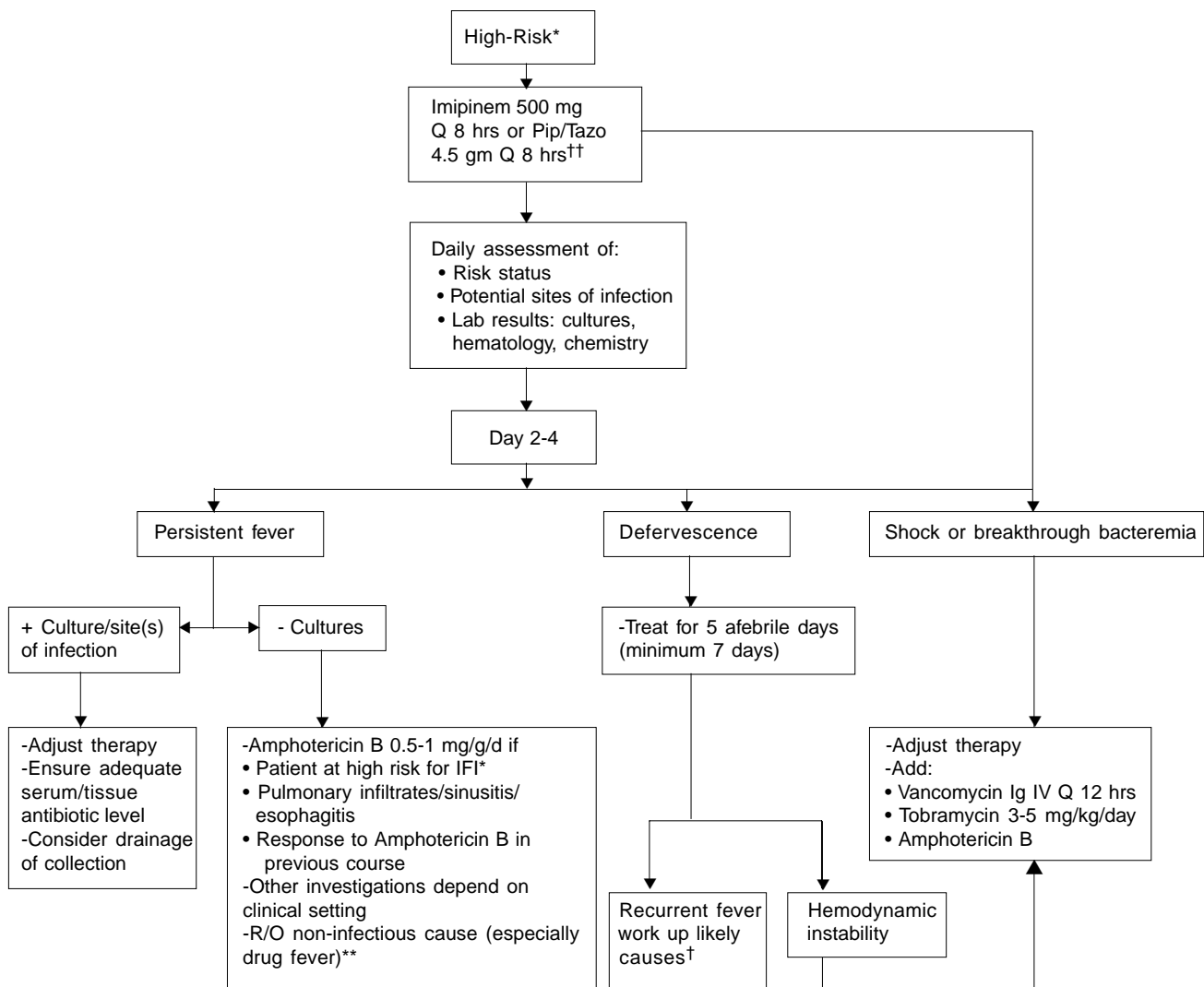
III. Treatment of Febrile Neutropenia

A. Risk-specific therapy

All febrile neutropenic patients should be treated empirically with broad-spectrum antibiotics. Given that no single regimen is superior to others, the choice of empiric therapy should depend on the risk group (high or low risk for complications), the pathogen likely to cause infection in a given setting, the potential sites of infection, the susceptibility patterns at a given institution, and the cost of the various regimens. A schematic approach is depicted in **Figures 1** and **2** and is based on the risk

Table 4: Likely causes of recurrent fever.

- Cytomegalovirus infection
- Chronic disseminated candidiasis (if no antifungal prophylaxis was given)
- *Clostridium difficile* colitis
- Non-infectious causes (especially drug fever)
- Respiratory viruses infection



* See Tables 1 & 3. Assumes patient is on antibacterial, antiviral and antifungal prophylaxis with a triazole.

** See Table 2

† See Table 4

†† Antibacterials given as recommended regimen. Other choices available (Table 5)

Abbreviations: Pip/Tazo: Piperacillin/ tazobactam; IFI: invasive fungal infection

Figure 2. Acute management of febrile neutropenia.⁽²⁾

for complications in a given patient (Table 3).

1. Standard inpatient therapy. Several regimens have been shown to be effective for the inpatient management of patients with febrile neutropenia. These include monotherapy (antipseudomonal β -lactam) and combination therapy (antipseudomonal β -lactam plus aminoglycosides, fluoroquinolones, and/or vancomycin) (Table 5).^(16,17)

The empirical addition of vancomycin is only warranted when the initial empirical regimen chosen does not offer appropriate coverage for the potentially fatal α -streptococcal infections (antibacterial agents such as piperacillin/tazobactam, imipenem and meropenem are effective against this pathogen).

Other therapeutic adjustments and follow-up after

48-72 hours of empirical antimicrobial therapy are outlined in Figure 2.

2. Outpatient therapy. Outpatient therapy may have several advantages over standard inpatient treatment, including improved quality of life, simplified antimicrobial therapy, and potentially lower cost and lower incidence of nosocomial spread of drug-resistant organisms.

Several risk factors have been identified as predictive of poor outcome among febrile neutropenic patients including history of prior hospitalization, active underlying disease, evidence of deep-organ infection, and presence of other co-morbid conditions such as hypotension, altered mental status, respiratory failure, dehydration, inadequate oral intake, gross bleeding, and others (Table 3). Patients with any of these high-risk conditions are

Table 5: Standard antibacterial regimens for empirical treatment of febrile neutropenia.

Empirical treatment	Drugs	Advantage	Disadvantage
Monotherapy	Antipseudomonal β -lactam*	Ease of administration Lower cost and toxicity (no aminoglycosides) No need for drug monitoring	Somewhat limited spectrum of antimicrobial activity
Combinations therapy	Antipseudomonal β -lactam + Aminoglycoside	Potential synergistic effect (doubtful clinical relevance) Broad spectrum activity (institutions with multidrug resistant gram-negative bacilli)	Higher costs and toxicity (aminoglycosides) Need for drug monitoring
	Antipseudomonal β -lactam + a Fluoroquinolone	Lower nephrotoxicity (no aminoglycosides) Better coverage for atypical bacteria (legionella, chlamydia, mycoplasma)	Increased incidence of quinolone resistant gram-negative organisms Higher costs and toxicity
	Double β -lactam regimens	Broad-spectrum activity (doubtful clinical relevance)	Increase in fungal superinfection Higher costs and toxicity
Any of the above + Vancomycin		Better gram-positive coverage particularly α -streptococcus if imipinem/cilaslatin or meropenem not in the selected regimen	Need for drug monitoring Risk of vancomycin-resistance Higher costs and toxicity

* Piperacillin/tazobactam, cefepime, ceftazidime, Imipinem/cilastatin, meropenem, others

Table 6: Host-specific Infections in patients with febrile neutropenia.

Therapy- / Host-related	Major immune defect	Pathogen commonly associated
Therapy-related		
Allo-SCT	Preengraftment	Neutropenia Bacteria: gram-positive, gram-negative Fungi: <i>Candida</i> , <i>Aspergillus</i> Viruses: HSV
	Immediate post-engraftment	Cellular and humoral immunity dysfunction Viruses: CMV Fungi: <i>Aspergillus</i>
	Late post-engraftment	Cellular and humoral immunity dysfunction Asplenia Bacteria: encapsulated Viruses: VZV
Auto-SCT	Preengraftment	Neutropenia Bacteria: gram-positive, gram-negative Fungi: <i>Candida</i> , <i>Aspergillus</i> Viruses: HSV
	Post-engraftment	Cellular and humoral immunity dysfunction Viruses: CMV, VZV
Purine analogues (fludarabine, 2-chloroxyadenosine, pentostatin) particularly when combined with corticosteroids	T cell dysfunction	Viruses: HSV, CMV, VZV Fungi: cryptococcus, moulds Bacteria: <i>Listeria monocytogenes</i> Parasites: <i>Pneumocystis carinii</i> Mycobacteria
High-dose cytarabine	Neutropenia, humoral and cellular dysfunction	Polymicrobial Typhlitis
Host-related		
T-cell leukemia	T cell dysfunction (mild)	Bacteria: chronic relapsing eczema associated with <i>S. aureus</i> and β -hemolytic streptococci Mycobacteria: tuberculosis and leprosy Parasites: Strongyloides, <i>P. carinii</i> Fungi: cryptococcus
Asplenia	Humoral immunity dysfunction	Bacteria: encapsulated Rarely intracellular parasites: Babesia, Malaria
Multiple myeloma and chronic lymphocytic leukemia	Humoral immunity dysfunction	Bacteria: encapsulated (recurrent) Complement dysfunction

Abbreviations: Allo-SCT, allogeneic stem cell transplantation; auto-SCT, autologous stem cell transplantation; PBSCT, peripheral blood stem cell transplantation; HSV, herpes simplex virus; CMV, cytomegalovirus; VZV, varicella-zoster virus; S, staphylococcus; P, pneumocystis

Table 7: Infections with rare organisms and treatment of choice

Pathogen	Treatment
Gram-positive bacteria	
<i>Listeria</i> spp.	Ampicillin, TMP/SMX
<i>Nocardia</i> spp.	Sulfonamides, TMP-SMX
<i>Leuconostoc</i> spp.	Penicillin/Ampicillin, Clindamycin, Erythromycin, Aminoglycoside
<i>Corynebacterium pseudodiphtheriticum</i>	According to antibiogram
<i>Corynebacterium striatum</i>	Susceptible to most antibiotics
<i>Corynebacterium equi</i> (Rhodococcus)	Erythromycin, Vancomycin, Imipenem, Ceftriaxone, Aminoglycosides
<i>Diphtheroid jeikeium</i>	Vancomycin
Gram-negative bacteria	
<i>Stenotrophomonas maltophilia</i>	TMP-SMX, Ticarcillin/clavulanate
<i>Yersinia enterocolitica</i>	Fluoroquinolones, Ampicillin, Aminoglycosides, Ceftriaxone, Ceftazidime
<i>Salmonella</i> spp.	Fluoroquinolones, TMP-SMX, Aztreonam, Ceftriaxone
<i>Plesiomonas shigelloides</i>	Fluoroquinolones, Cefotaxime, Aminoglycosides
<i>Vibrio</i> spp.	Fluoroquinolones, TMP-SMX
<i>Aeromonas</i> spp.	TMP-SMX, Fluoroquinolones, Aminoglycosides, Aztreonam, Imipenem, third-generation cephalosporins
<i>Capnocytophaga</i> spp.	Penicillin, Susceptible to most antibiotics
Spirochetes	
<i>Borrelia</i> spp.	Penicillin, Tetracycline
<i>Treponema</i> spp.	Penicillin
<i>Ehrlichia</i>	Tetracycline, Chloramphenicol
Yeasts	
<i>Candida krusei</i>	Am B*
<i>Torulopsis glabrata</i>	Am B*
<i>Trichosporon</i> spp.	Fluconazole (high dose) Am B*
Endemic fungi	
<i>Histoplasma</i> spp.	Am B*, Itraconazole
<i>Coccidioides immitis</i>	Am B*, Itraconazole, fluconazole
<i>Paracoccidioides</i> spp.	Am B*, Itraconazole
Moulds	
Zygomycetes	Am B*, Surgery
Phaeohyphomycoses	Surgery
<i>Curvularia</i>	Am B*
<i>Alternaria</i>	Itraconazole
<i>Exserohilum</i>	
<i>Bipolaris</i> spp.	
Hyalohyphomycoses	Surgery
<i>Fusarium</i> spp.	Itraconazole/Fluconazole
<i>Scedosporium</i> spp.	Miconazole
<i>Scopulariopsis</i>	
Parasites	
<i>Leishmania</i>	Am B*, Rifampin
<i>Toxoplasma</i>	Pyrimethamine-Sulfonamides, Pyrimethamine-Clindamycin
<i>Strongyloides</i>	Thiabendazole, Ivermectin
<i>Giardia intestinalis</i>	Metronidazole
<i>Mycobacterium tuberculosis</i>	Isoniazid, Rifampin, Pyrazinamide, Ethambutol, and/or Streptomycin
Atypical mycobacteria	
<i>Mycobacterium avium intracellulare</i>	Clarithromycin, Azithromycin, Ethambutol, Rifabutin, Ciprofloxacin, Amikacin, doxycycline
<i>Mycobacterium fortuitum</i>	
<i>Mycobacterium chelonae</i>	

*AmB: Amphotericin B or lipid formulations

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; GI, gastrointestinal; RSV, respiratory syncytial virus; HHV-6, human herpesvirus-6; URTI, upper respiratory tract infections

more likely to have serious medical complications (>30%) than patients without any risk factors (<5 %) and to have more than 10% mortality (as opposed to almost no mortality among the low risk patients). Thus low risk patients could be treated as outpatients (Figure 1).

Successful outpatient therapy requires stabilization of the patient's clinical status and education of the patient and family. The patient's home environment is also an important variable to consider when selecting outpatient therapy for patients with hematological malignancies (Table 3).

The agents of choice for outpatient therapy include the quinolones (particularly levofloxacin, provided the patient has not been on quinolone prophylaxis), the glycopeptides (vancomycin and teicoplanin), ceftriaxone, and the aminoglycosides (given once daily).^(18,19)

B. Site-specific therapy

The common sites of infections in neutropenic patients are the oral cavity and esophagus, upper and lower respiratory tract, skin and soft tissue, perianal region, and urinary and gastrointestinal (GI) tracts. Non-infectious causes can mimic these syndromes and should be included in the differential diagnosis of febrile neutropenia (Table 2).

C. Host-specific therapy

While the approach described above applies to all neutropenic patients, some populations are particularly vulnerable to certain infections: allogeneic SCT recipients, patients with multiple myeloma or T-cell leukemia, those previously treated with fludarabine or other purine analogs,⁽²⁰⁾ and patients who have been splenectomized (Table 6). In such patients, one should consider the most common pathogens in these populations at risk when considering empirical coverage.

D. Organism-specific therapy

Additional antimicrobial agents may be needed once a pathogen has been identified. It is important to keep in mind that patients with hematological malignancies are likely to be infected with more than one organism. Thus, broad-spectrum coverage (bacterial, viral, fungal) needs to be continued depending on the clinical setting. Newly recognized pathogens may also cause infection in patients with hematological malignancies. A selected list is shown in Table 7.

IV. Special issues

A. Antimicrobial-coated central venous catheters:

Where are the data?

There are conflicting data on whether or not antimicrobial-coated central venous catheters (ACVC) have cost-

effective benefits in preventing CVC-related bloodstream infections (BSI). Two of twelve randomized trials comparing the efficacy of ACVC to uncoated control CVC among patients at high-risk for BSI (intensive care unit, solid organ transplant, bone marrow transplant, and patients receiving total parenteral nutrition) showed a significant reduction in CVC-related BSI with ACVC when compared to uncoated CVC. In only one of these two studies did the difference remain significant when bacteremias due to skin contaminants such as coagulase-negative staphylococci were excluded. However, none of the studies showed a significant reduction in the clinically relevant endpoints of antibiotic use, length of hospital stay, or mortality.

Furthermore, through the use of molecular techniques, there is evidence that a sizable number of these organisms (including coagulase-negative staphylococci) originate in the gastrointestinal tract and not from the skin.⁽²¹⁾ Thus, coating CVC catheters with antimicrobial agents is unlikely to be clinically useful, and a major concern of their use is the rise in antimicrobial resistance. Therefore, ACVC cannot be recommended on the basis of published literature.

B. Respiratory viral infections: False alarm on respiratory syncytial virus

Respiratory viral infections (RSV, influenza viruses, parainfluenza viruses, adenovirus, rhinovirus, others) are not uncommon among immunosuppressed patients but are rarely consequential.⁽²²⁾ Although concerns have been raised about the major risk posed by one of these organisms (RSV) and the use of ribavirin and intravenous immunoglobulins has been advocated,^(23,24) recent data from our center indicate that RSV is likely to be a colonizer and rarely associated with serious infections.⁽²²⁾

C. Cellular therapy: Promising

Transfusion of granulocytes obtained from a healthy donor may be beneficial in treating infections in neutropenic patients. Cytokines such as granulocytes and granulocyte-monocyte colony-stimulating factors (G-CSF, GM-CSF) have been shown to stimulate sustainable granulocyte increases leading to a higher yield of cells. Early results obtained with transfusion of white blood cells from G-CSF-stimulated donors to profoundly neutropenic patients with fungal infections are promising.⁽²⁵⁾

D. Cytokines: Useful in certain settings

The prophylactic use of colony-stimulating factors (CSFs) is recommended only in settings when the risk of febrile neutropenia is >40%. The addition of CSFs to the antimicrobial regimen in febrile neutropenia has not proven useful,⁽²⁶⁾ although cytokines may be beneficial in the setting of documented infection.⁽²⁷⁾

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