

68 Infections in the Immunocompromised Host

Ibrahim Bin-Hussain

Introduction

Infections are considered a major cause of morbidity and mortality in immunocompromised children. The survival rate in this particular population has increased over the last 3 decades. This is mainly due to the advancement in medical technology leading to improvement in diagnosis capabilities as well as supportive care including antimicrobial therapy.

Immunodeficiency can be divided into primary and secondary immunodeficiency disorders. Primary immunodeficiency disorders including combined T-cell and B-cell immunodeficiencies, antibody deficiency, disease of immune dysregulation, congenital defects of Phagocyte number or function or both, defects in innate immunity, autoimmunity disorders, complement deficiencies, and cytokine defects. Secondary immunodeficiency disorders include human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) – both of which lead to altered cellular immunity – dysgammaglobulinemia, defective phagocytic function or neutropenia. Cancer leading to neutropenia, lymphopenia, humoral deficiencies and altered physical integrity especially with the use of chemotherapeutic agents leading to disruption barrier integrity with mucositis leading to easy access of microorganisms, solid organ transplant leading to deficiencies in cellular and phagocytic immunity, malnutrition which leads to impaired immunity, and complement activity.

Fever is the main manifestation and occasionally the only sign of infection in immunocompromised children. When approaching a patient with immunodeficiency in the context of infection, one needs to look at the net state of immunosuppression. The net state of immunosuppression can be evaluated by the host defense defects caused by the primary disease, dose and duration of the immunosuppressive therapy (the longer duration of immunosuppressive therapy, the higher risk of infection), presence of neutropenia, and anatomical and functional integrity because defect in the skin or mucosa can lead to easy access for the microorganisms, metabolic factors, and infection with immunomodulating viruses (HIV, HBV, HCV, CMV, EBV, and HHV-6).

Risk of infections can be classified as high, intermediate, and low. High risk includes hematologic malignancies, AIDS, HSCT, splenectomized patient, and congenital immunodeficiency especially severe combined immune deficiency (SCID). Intermediate risk includes solid tumors, HIV/AIDS, and solid organ transplantation. Low-risk patients include patients with corticosteroid therapy, local defects, and diabetes.

Etiology

The pathogens in immunocompromised patients can be predicted based on the immune defect. For example, if there is an anatomical disruption in the oral cavity it lead to infections caused by alpha hemolytic streptococci, anaerobes, *Candida* species, and herpes simplex virus (HSV). Patients with urinary catheters will be at risk for infection caused by gram negative bacteria including *Pseudomonas* spp., enterococci, and possibly candida. If there is a skin defect including central venous catheter (CVC), the patient will be at risk of *Staphylococcus* species (both coagulase-negative *staphylococci* and *Staphylococcus aureus*, *Bacillus* species, atypical *Mycobacterium*, and Gram-negative organism. If a defect in the phagocytic function, either quantitative or qualitative, predispose what to invasive diseases like invasive pneumonia caused by bacterial pathogens: Gram-positive (staphylococci, streptococci, and *Nocardia* species) and Gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, *P. aeruginosa*), other enterobacteriaceae, and fungal pathogens like *Candida* species and *Aspergillus* species.

Patients with defective cell-mediated immunity are at risk of infections caused by intracellular pathogens (i.e., viral, fungi, mycobacterial, and intracellular bacteria). Intracellular pathogens include *Legionella* species, *Salmonella* species, *Mycobacteria*, and *Listeria* species, *Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Candida* species, *Pneumocystis jiroveci*, cytomegalovirus, Varicella-zoster virus, Epstein-Barr virus, live viral vaccines (measles, mumps, rubella, and

polio) and protozoal, *Toxoplasma gondii*, *Strongyloides stercoralis*, *Cryptosporidia*, *Microsporidia*, and *Isospora* species.

Patients with immunoglobulin deficiency are at risk of sinopulmonary infection caused by *S. pneumoniae*, *Haemophilus influenzae*, and CNS infection from viral infections, especially enterovirus, leading to chronic meningoencephalitis as well as gastrointestinal infection due to giardiasis. Patients with complement deficiency are at risk of diseases caused by *S. pneumoniae*, *H. influenzae*, and *Neisseria* species. Splenectomized patients are at risk of invasive diseases (e.g., sepsis, meningitis) caused by encapsulated organism including *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*.

In evaluating patients with immunodeficiency, one can predict the pathogen based on the primary immune defects, the organs involved, and the clinical presentation of the patient. For instance, *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Pseudomonas* and *aspergillus* infection should be considered for a chronic granulomatous disease (CGD) patient with soft tissue infection, lymphadenitis, liver abscess, osteomyelitis, pneumonia, and sepsis.

Diagnosis

In centers dealing with immunocompromised patients, the microbiology laboratory as well as the radiology service need to be well equipped and trained in diagnosing these patients. Patients with fever should be worked up with complete blood count with differential, renal, and hepatic profile, blood culture from central line (if present), and peripheral culture. Chest X-rays are not done routinely unless the patients have respiratory symptoms. Other investigations need to be guided by the presentation of the patient. Patients with diarrhea should have stool checked for bacterial culture, ova and parasite, viral culture, rotavirus, and electron microscopy for viral studies, in addition to microspora, cryptosporidium, and isospora. In addition to chest X-ray, patients with respiratory symptoms required nasopharyngeal aspirate for rapid test for viruses and PCR multiplex – a newly developed laboratory procedure that can screen multiple viruses and other respiratory pathogens in the same setting. Patients with skin lesions should have skin biopsy from the lesion, which will be sent for culture (bacterial, fungal, and mycobacterium) in addition to histopathology for Gram-stain and special staining for fungal as well as acid fast stain (AFB stain).

Management

There are several objectives in managing infections in immunocompromised patients. The first and foremost objective is to assure patients' survival and prevent infectious morbidity. Decrease days of hospitalization and decrease exposure to multidrug resistance organism, decrease number of days of antibiotic use to minimize selection of resistance organism. Modification of antimicrobial therapy in immunocompromised patients is the rule rather than the exception. Timely modification of antibiotic therapy is very important to control breakthrough infection.

There are several questions to be addressed to choose the effective antimicrobial therapy when evaluating patients. In addition to history and physical examination, it is important to determine which arm/arms of the immune systems that is/are affected? what the clinical syndrome/site of infection is? (to predict what are the likely pathogens), what clinical specimen(s) should be obtained (empiric/definitive therapy)? and which antimicrobial agents have predictable activity against pathogens? With these in mind, one can predict pathogen and choose the right antimicrobial agents.

Patients with Wiskott–Aldrich syndrome are at risk of bacterial pneumonia as well as sepsis with Gram-positive organisms including MRSA. In this situation, medication should include agents active against Gram-negative pathogen plus anti-staphylococcus agents, for example, cefotaxime or ceftriaxone plus nafcillin; if MRSA or penicillin resistant *S. pneumoniae* is suspected, one can use vancomycin.

The pathogen in immunocompromised patients can be predicted by the system involved during the presentation. For example, the presentation and etiological agents in pneumonia in immunocompromised patients are different than immunocompetent persons. In evaluating pneumonia in immunocompromised patients, one needs to know that the pulmonary complication is present in up to 60% of immunocompromised patients and mortality is up to 80% of those who require mechanical ventilation. The initial evaluation needs rapid assessment of the vital signs including oxygen saturation, complete blood count with differential, renal profile, blood culture, and imaging of the lung either chest X-ray or CT scan. The organism can be predicted based on the primary immune defect. At certain point in the history, the defect in the immune system, the presence or absence of neutropenia, history of antimicrobial exposure, the presence of potential pulmonary pathogens in previous cultures, and the presence of indwelling catheters should be looked at.

The pattern and distribution of radiological abnormalities can predict the pathogen and the time and the rate of progression and time to resolution of pulmonary abnormalities.

For definitive diagnoses invasive procedures may be needed including bronchoalveolar lavage (BAL), transbronchial biopsy, needless biopsy, thorascopic biopsy, and open lung biopsy. In obtaining the biopsy from this patient, it is very important to send it for histopathology for special staining, for viruses, bacteria, fungi, pneumocystis, mycobacterial pathogen, and also culture for viral, fungal, bacterial, and mycobacterium.

Other laboratory tests that will help in diagnosing pneumonia are nasal washings or swabs for direct fluorescent antibody, PCR for respiratory viruses and atypical pneumonia, culture and staining, CMV antigenemia or CMV viral load testing, *Aspergillus* galactomannan assay, and 1,3 beta D glucan.

The radiological finding in immunocompromised patient can be focal (lobar or segmental infiltrate), diffuse interstitial infiltrate or nodular (with or without cavitation). Focal infiltrate can be due to Gram-positive or Gram-negative bacteria, *Legionella*, mycobacteria, and fungal infection. Also the noninfectious etiology includes infarction, radiation, and drug-related bronchiolitis obliterans organizing pneumonia (BOOP). Diffuse interstitial infiltrate is caused by viral infection, *Pneumocystis jiroveci*, less likely mycobacterium, disseminated fungal infection, atypical pneumonium including *Chlamydia*, *Legionella*, and *mycoplasma*. Other noninfectious etiology causing diffuse interstitial infiltrate include edema, acute respiratory distress syndrome (ARDS), and drug-related radiation. For nodular infiltrate with or without cavitation the infectious etiology include *Aspergillus* infection, and other mycoses, *Nocardia*, bacteria either Gram-positive or Gram-negative, anaerobes, and *Mycobacterium* TB, as well as noninfectious etiology including disease progression like metastasis and drug toxicity.

The management of immunocompromised patients with pulmonary infiltrate will depend on the patient presentation. If the patient is acutely ill, it is very important to begin empiric therapy to cover the likely pathogen based on the presentation of the patient and the primary immune defect with simultaneously comprehensive evaluation.

Subsequently, therapy should be adjusted based on culture and clinical response. In providing empirical antibiotic therapy in patient with pulmonary infiltrate and defect in cell-mediated immunity one need to consider *Pneumocystis jiroveci*, nocardia, legionella, mycoplasma, in addition to aerobic Gram-positive cocci and

Gram-negative bacilli therefore it is advised to use trimethoprim-sulfamethoxazole, macrolides including erythromycin or clarithromycin and agent active against Gram-positive and Gram-negative; for example, third-generation cephalosporin with or without aminoglycoside with anti-Gram-positive either nafcillin or vancomycin based on the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin resistant *Streptococcus pneumoniae*.

Infection in Cancer Patients with Fever and Neutropenia

The fever is defined in the context of febrile neutropenia as a single oral temperature of more than 38.3°C or more than 38.0°C for at least 1 h and is not related to the administration of pyrexial agents including blood, blood product, IVIG, and pyrogenic drugs, especially Ara C.

Neutropenia is defined as absolute neutrophil count (ANC) less than 500/mm³ or less than 1,000/mm³ with predictive decline to less 500/mm³ 48 h.

Risk Factor for Infection in Cancer Patients

The most important risk factor is the presence of neutropenia as well as the degree and duration of neutropenia. The lower the neutrophil count, the higher the risk of infection. The longer the duration of neutropenia, the higher the risk of infection. Usually, neutropenia is considered high risk if ≥ 7 days and low risk < 7 days. Other risk factors include associated medical comorbidity, primary disease, and status (remission or relapse). Low-risk patients are clinically defined by neutropenia as anticipated lasting less than 7 days, clinically stable, and having no medical comorbid conditions.

Epidemiology

About 50% of neutropenic patients who become febrile have established or occult infections and about 25% of patients with ANC less than 100 cells/mm³ have bacteremia.

The risk varies depending on the underlying disease, for example, patients post allogenic bone marrow transplantation are at higher risk than autologous bone marrow transplantation while AML has the higher risk than ALL. The lowest risk is in patients with cyclic neutropenia.

Evaluation

In evaluating a patient with fever and neutropenia, it is important to keep in mind that signs and symptoms can be muted or subtle. Profoundly neutropenic patients can sometime have life-threatening infections and yet be afebrile especially if they presented with abdominal pain. Careful and comprehensive physical examination is critical and should be repeated at least daily because these patients are dynamic and their condition can change rapidly.

Other important points in the history include the nature of chemotherapeutic agents, steroids, or other immunosuppressive agents because these can predict the degree of immunosuppression, the duration of neutropenia, and the severity of neutropenia. The history of antibiotic prophylaxis is also important because the antibiotic used as prophylaxis should be avoided in treating these patients. Reviewing the recent documented infection with susceptibility can help in determining the empiric therapy. For example, if the patient has a previous infection with multidrug resistance pathogen, empiric therapy can be used to cover these pathogens. If the patient had recent surgical procedure, this means there is break of the skin and is at risk for certain pathogens including Gram-positive cocci (coagulase negative *Staphylococci* and *Staphylococcus aureus*). Allergy history is an important factor in selecting empirical therapy as allergic medications need to be avoided.

Detailed and thorough physical examination is important with focus on certain sites that can be a portal of entry of pathogens including periodontium, pharynx, lower esophagus, lung, skin, perineum, bone marrow aspiration site, and catheter entry and exit sites.

After history and thorough physical examinations, blood culture from central and peripheral lines should be done in order to identify the source of infection. For example, if the blood culture is positive from the central culture but negative from peripheral culture, the likely source is the central line. If both are positive, time is needed to positively determine the source of infection. Routine surveillance culture is not indicated as it is not cost effective and has low predictive value. Other cultures should be guided by the sites of infection. For example, a patient with respiratory symptoms needs to have nasopharyngeal aspirate for viral study, PCR multiplex, and atypical pneumonia. Patients with gastrointestinal symptoms, for example, with diarrhea, the stool needs to be sent for viral study, culture and sensitivity, ova and parasite. Chest X-ray should not be done routinely in all patients with fever and neutropenia because it has low yield in patients without respiratory symptoms. It is only

done in children who have respiratory symptoms. If negative, a chest CT scan to be considered to better evaluate patient not responding to therapy.

Site of Infection

Most patients with fever and neutropenia have no identifiable site of infection and no positive culture results. Bloodstream infection is documented in about 20% of patients with fever and neutropenia. Disruption of the skin or soft tissue including vascular access or catheter insertion site can be a point of entry. In those centers, who are dealing with cancer patients, it is very important to monitor the infection rate and pathogen as well as the resistance pattern in the same center. The local data will help to select the appropriate empirical antimicrobial therapy (● [Table 68.1](#)).

Management

There is no ideal regimen because there are variables which include the risk status of the patient, microflora and their sensitivity patterns, toxicity indication, preference, and the cost. Prompt initiation of broad-spectrum therapy when neutropenic patients became febrile is the key to successful management. In 1960 the mortality rate was up to 80% initially but with the introduction of empiric therapy against gram-negative organism the mortality rate now is close to 5%. There is no ideal regimen because this can be determined based on the isolate and its susceptibility in the same center as each center for example, one cannot extrapolate from different centers the likely pathogen, the same thing that a center can have a different pathogen and different susceptibility pattern in adult versus pediatric population with febrile neutropenia (● [Table 68.2](#)).

Monotherapy Versus Combination Therapy

Monotherapy and combination therapy has equal efficacy. The monotherapy needs to have antipseudomonal activities including antipseudomonal penicillin with or without beta-lactamase inhibitor, carbapenem, and third- or fourth-generation antipseudomonal cephalosporins. The combination therapy includes antipseudomonal beta-lactam with Aminoglycoside. Both monotherapy and combination therapy have equal efficacy but it is important to look at the local data to be able to predict the empiric therapy either combination therapy or monotherapy.

Table 68.1

Common bacterial pathogens in neutropenic patients

Common Gram-positive pathogens
Coagulase-negative staphylococci
<i>Staphylococcus aureus</i> , including methicillin-resistant strains
<i>Enterococcus</i> species, including vancomycin-resistant strains
Viridans group streptococci
Streptococci pneumonia
<i>Streptococcus pyogenes</i>
Common Gram-negative pathogens
<i>Escherichia coli</i>
<i>Klebsiella</i> species
<i>Enterobacter</i> species
<i>Pseudomonas aeruginosa</i>
<i>Citrobacter</i> species
<i>Acinetobacter</i> species
<i>Stenotrophomonas maltophilia</i>

It is worth stressing that vancomycin should not be used routinely for empiric therapy in febrile neutropenia and there is a special indication for vancomycin. The vancomycin indication includes hemodynamic instability or other evidence of severe sepsis, pneumonia documented radiographically, positive blood culture for gram-positive bacteria before final identification and susceptibility testing is available, clinically suspected catheter-related infections (e. g., chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site), skin or soft-tissue infection at any site, colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae*, and severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy. If the patient started empirically on vancomycin the need for continuation of vancomycin should be re-assessed on daily basis. Overuse of vancomycin in more than 90%, and selection for resistant organism and emergence of vancomycin resistance enterococci.

The factors influencing antimicrobial selection include the types of bacterial isolates found in the institution, antibiotic susceptibility patterns, drug allergies, presence of organ dysfunction, chemotherapeutic regimen whether the patient was receiving prophylactic antibiotics, and condition of the patient at diagnosis, for example, presence of signs and symptoms at initial evaluation and presence of documented sites requiring additional therapy.

Table 68.2

Recommendation from Clinical Practice Guidelines for empirical initial therapy in neutropenic patients with fever

Guidelines	Monotherapy	Combination therapy
IDSA (Infectious Disease Society of America), Freifeld et al. CID 2011	High Risk:* Cefepime Imipenem-cilasiatin Meropenem Piperacillin-tazobactam	Low Risk:
NCCN (National Comprehensive Cancer Network) 2008	Ceftazidime Cefepime Imipenem-cilasiatin Meropenem	Aminoglycoside+ antipseudomonal penicillin Aminoglycoside+ extended spectrum cephalosporin Ciprofloxacin + antipseudomonal penicillin
IHQ (infectious Diseases Working Party of the German Society of Hematology and Oncology) Link et al. 2003	Piperacillin-tazobactam Ceftazidime Cefepime Imipenem-cilasiatin Meropenem	Aminoglycoside+ acylaminopenicillin Aminoglycoside+ third- or fourth-generation cephalosporin
SEQ (Chemotherapy Society of Spain), 2001	Cefepime Meropenem	Not recommended for routine use

*Other antimicrobials (aminoglycosides, fluoroquinolone, and/or vancomycin) may be added to initial regimen for complicated presentation or if resistance is suspected or proven

The center-specific factors include the patterns of resistance, effect on microbial ecology, high presence of vancomycin resistance enterococci (VRE), or extended spectrum beta-lactamase (ESBL) producing organism. The patient-specific factors including recent antibiotic use such as current prophylaxis as drug allergy, and the underlying organ dysfunction. The signs and symptoms present at the initial evaluation determine.

In the recent year more interest in the outpatient therapy for patient with fever and neutropenia. The advantages of ambulatory management of febrile patients with neutropenia especially those at low risk include lower cost particularly with oral outpatient therapy, fewer superinfections caused by multidrug-resistant nosocomial pathogens, improved quality of life for patient, greater

convenience for family or other caregivers, and more efficient utilization of valuable and expensive resources. The disadvantage includes the potential risk for developing serious complications such as septic shock at home, risk of noncompliance particularly with oral therapy, false sense of security or inadequate monitoring for response to therapy or toxicity, and the need to develop a team and infrastructure capable of treating substantial numbers of low-risk patients.

There are several requirements for successful outpatient treatment programs for patients with febrile neutropenia which include institutional infrastructure and support, a dedicated and experienced team of health-care providers, availability of institution-specific epidemiological data and susceptibility and resistance data, microbiologically appropriate treatment regimen, frequent follow-up monitoring of outpatient, adequate transportation and communication capabilities, and access to management team 24 h a day, 7 days a week.

Modification of Therapy

There are certain clinical events or manifestations that require modifying the initial antimicrobial therapy; for example, if a patient has breakthrough bacteremia and if Gram-positive is isolated (add vancomycin especially if there is a risk of MRSA or pneumococcal resistance penicillin). If Gram-negative organism is isolated consider resistant Gram-negative and can change the regimen or broaden the coverage (carbapenems if the data in the center showed that the carbapenems has better sensitivity than cephalosporin or beta-lactam antibiotic). If the patient has catheter-associated soft tissue infection, vancomycin should be added. Patients with severe oral mucositis or necrotizing gingivitis are at risk of anaerobic bacteria as well as viruses; add agent that is active against beta-lactamase-producing anaerobic bacteria including clindamycin, metronidazole, and acyclovir should be considered. If the patient has diffuse pneumonia, continue with the broad-spectrum anti-Gram-negative coverage (add trimethoprim-sulfamethoxazole and macrolide to the therapy). Increasing neutrophil count on patients who developed new infiltrates while on antibiotic can be related to the recovery of neutropenia. If the patient is stable observe if the neutrophil count is not rising, antifungal therapy should be considered as the patient is at risk for fungal infection. In addition to other evaluation *Aspergillus* galactomannan and B-D glucan (fungitell) should be done with chest CT scan. Depending on the CT scan findings bronchoalveolar lavage or lung

biopsy should be considered. Patient with prolonged fever and neutropenia needs to be observed if recovery of neutropenia is not imminent. Antifungal therapy can include either regular amphotericin B, or lipid formulation of amphotericin B including liposomal amphotericin B (amBisome) or amphotericin B lipid complex (ABLCL), caspofungin or voriconazole depending of the availability of medications and epidemiology of the institution.

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