Fever in the Immunocompromised Host

Mangesh Tiwaskar

The past two decades have witnessed an increase in the number of patients who are immunocompromised as a consequence of a primary or secondary immunodeficiency disorder or from the use of agents that depress one or more components of the immune system. The immunocompromised patient is at risk for developing a wide variety of life-threatening infectious diseases. Depending on the underlying immune system defect, many diverse microbes, including those handled routinely by the immunocompetent host, can become pathogens. Immunocompromised patients can have the same infections as immunocompetent people but in addition one needs to consider some more specific infections which are especially found in immunocompromised host. Patients who are immunocompromised for whatever reason are liable to contract opportunistic infections. Broadly defined, an immunocompromised host has an alteration in phagocytic, cellular or humoral immunity that increases the risk of an infectious complication or an opportunistic process such as a lymphoproliferative disorder or cancer. Patients may also be immunocompromised if they have an alteration or breach of their skin or mucosal defence barriers that permits microorganisms to cause either a local or a systemic infection, e.g. from burns or indwelling catheters, etc.

Fever in the immunocompromised host is generally defined as a single reading over 38.3°C or a temperature over 38°C for a period of 1 hour or more. Fever is often the sole finding, and the incidence of serious disease in this group of patients is high. HIV disease, transplant medicine, cancer therapy and rheumatologic therapy have contributed to the increased prevalence of immunocompromise in the general population. Although a number of fever patterns have been associated with various infectious or noninfectious illnesses, no pathognomonic pattern or degree of fever has been clearly associated with a specific infection in immunocompromised patients. There is also no pattern of fever that can be used to rule out a noninfectious cause. Furthermore, patients who are profoundly immunocompromised can (albeit rarely) have serious local or systemic infections in the absence of fever. Fever can also be suppressed or muted by immunosuppressive agents that may be part of the therapeutic regimen, especially steroids and non-steroidal anti-inflammatory agents. However, patients with infection usually have fever despite the use of these agents.

Fever is a manifestation of the release of proinflammatory cytokines (interleukin-1α, interleukin-1β, interleukin-4, interleukin-6, and tumor necrosis factor-α) from macrophages, lymphocytes, fibroblasts, epithelial cells and endothelial cells as a consequence of infection or inflammation. Analogues of these cytokines are inherent in the innate immune response throughout phylogeny as well as being part of the acquired immune system that confers antigen-specific immune defence. Although endogenous pyrogens are classically thought to originate from polymorphonuclear leucocytes (PML), patients with profound neutropenia have high fevers when they have infections, so reservoirs of pyrogens other than neutrophils are also important.

One of the most important decisions with respect to an immunocompromised patient is whether a fever requires urgent evaluation and prompt empirical antimicrobial therapy. We should develop a systematic approach for patients with compromised immune systems who present with fever, including historical and physical findings pertinent to these patients, with attention to details that are atypical or specific to the immunocompromised state; a diagnostic work-up applicable to most patients with immune system dysfunction; a knowledge of common clinical scenarios of immunosuppression, focusing on unique presentations and treatment strategies. Although the causes of fever in immunocompromised hosts are numerous, some guidance is given by the specific immunologic defect or defects present in the patient. In addition, the length of time that the immune defences are altered has an extremely important effect on the types of infectious complications that are likely to occur. Among the clinical conditions associated with a risk of life-threatening infections are profound neutropenia (i.e. an absolute neutrophil count of less than 500/ml) or a history of splenectomy. In patients with these characteristics, rapidly progressive infection may be life-threatening if untreated. Because of the blunted inflammatory response in patients with neutropenia, the signs and symptoms of infection can be minimal, so a heightened index of suspicion for infection is essential. Patients, in whom neutropenia develops after a viral infection, do not have the same risk of acute bacterial infection, as those who have neutropenia after chemotherapy or preparative therapy for transplantation. Presumably this is because they do not have concurrent breaches of mucosal integrity. Similarly, although patients with aplastic anaemia or congenital neutropenia are vulnerable to acute bacterial infections, they are generally at lower risk for the acute life-threatening bacterial infections seen in patients who have neutropenia after cytotoxic chemotherapy. The development of fever in a HIV-infected patient who also has neutropenia suggests the possibility of an infectious complication.

Recognizing that this brief review cannot be comprehensive, the author will try to highlight some of the specific issues and challenges in the management of fever in immunocompromised patients, focusing on infectious complications. It must, of course, be remembered that fever can also be due to noninfectious causes such as drugs, certain cancers, inflammation, vasculitis, etc.

THE IMMUNE SYSTEM
The immune system is a complex, multiorgan network that protects the body from pathogenic invasions by microbes. When part of
the immune system functions in a compromised state, infectious complications can be sudden and fulminant. A defect at one site in the system can elicit dysfunction throughout the system. Although a detailed review of immune system function is beyond the scope of this article, understanding the basic components and their basic interactions facilitates management of immunocompromised patients by providing a diagnostic framework.

Host defences include various physical barriers, such as skin, mucosa, secretory substances, and normal flora. The complexity of the system increases greatly at the level of cellular and molecular defense mechanisms. Lymphocytes perform a variety of functions central to competent immune function. B lymphocytes produce immunoglobulins that are critical for phagocytosis, bind to bacterial toxins, and prohibit microorganism entry from respiratory and alimentary tracts. T lymphocytes are the primary effectors of cell-mediated immunity. Some of the T cells become cytotoxic killer cells able to lyse infected host cells or foreign cells. Other T cells regulate a host of immune responses by producing various agents, collectively known as lymphokines (e.g. interferon-γ, tumour necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF)) that serve to activate and modulate macrophages, B lymphocytes, and other T lymphocytes.

Phagocytic cells ingest and destroy bacteria, fungi, and some large viruses; they also serve as activation centers for other components of the immune response. Phagocytic cells are either fixed or mobile and are widely distributed throughout the body. Mobile cells include granulocytes and monocytes. Fixed cells are primarily macrophages, including some specialized types, such as alveolar cells, Kupffer cells, and spleen and lymph node histiocytes. The spleen provides a site for the phagocytosis of intravascular pathogens and for the initial antibody synthesis in response to intravenous antigens. Additional functions include production of humoral factors (complement proteins) and coordination of B cell/T cell interaction. The complement cascade and other inflammatory response mediators (e.g. bradykinins, fibrinolytic system) are also involved in competent immune function, integrating and accelerating the immune response and recruiting additional cellular and molecular help.

Once mature, T and B lymphocytes and monocytes enter the circulation and travel to peripheral lymphoid tissue (e.g. lymph nodes, spleen and gut-related sites) where they await activation by a foreign antigen. Typically, the lymphocytes measured on a complete blood count are composed of about 80% T cells and 15% B cells. Mature granulocytes (e.g. neutrophils, eosinophils, and basophils) also circulate in the peripheral blood and tissues, becoming active at sites of inflammation. The details of the immune system activation and response are beyond the scope of this article.

HISTORY AND PHYSICAL EXAMINATION

The symptoms and signs of infection that can be present in any given compromised host span a wide spectrum. When a patient’s ability to respond to infectious insult is blunted, fever is often the sole complaint and the precipitating event. The physical examination can be “normal” or reveal a mild tachycardia or other subtle signs. The absence of a classic infectious presentation beyond fever should not deter the emergency physician from aggressive, expedient work-up and treatment.

The presence of fever elicits an automatic infectious disease differential; however, a significant number of immunosuppressed infected patients present with confusion or other vague complaints, such as a lack of well-being. Patients without fever but with infection might remain undiagnosed. Fever in the immunocompromised host follows the normal diurnal pattern that temperatures follow in the healthy adult, typically lower in the mornings, with a peak in temperature around 4 PM. The history should include the criteria as per Table 1.

The history should include a review of the immunocompromised state: duration of immunocompromise; past infections, and current and previous therapies, especially chemotherapy; and immunosuppressive drugs and antibiotics. In patients with a history of fungal infection, recurrence is frequent if no prophylaxis is given after acute treatment. A history of long-term broad-spectrum antibiotic use also predisposes to fungal infection. Patients with a history of CMV and Herpes simplex have high reactivation rates in the immunocompromised host. A history of transfusion should add related diseases (hepatitis B and C, cytomegalovirus, malaria, Epstein-Barr virus) to the differential diagnosis. Some patients do not know their medical histories or drug regimens well enough to stay alert.

Eliciting acute symptoms beyond fever can be difficult, and seemingly minor complaints can point the way to major infections. Pain in isolation of other symptoms can be the first warning of localized infection and should be vigorously pursued. The patient may be able to identify new skin lesions that help to identify a pathogen. Gastrointestinal (GI) symptoms are common in patients with cancer and can be caused by acute infection, such as with esophagitis or sepsis, or by the primary disease process or its treatment. Pulmonary symptoms are common in patients with an infiltrate definable by initial chest radiograph. Sinus symptoms, especially in neutropenic patients, should be noted and pursued.

The physical examination should be complete, because the findings present for a given infection can be subtle. Common sites of infection should be examined thoroughly. The intraoral examination should search for necrotizing gingivitis or ulcerative lesions. Non-pruritic nasal discharge, pale areas of mucosa and patches of mucosal hyperesthesia can represent sinusitis. Black eschars on the palate or nasal mucosa can signify the presence of mucormycosis, and they are sometimes confused with clots from a bleeding disorder.

Examination of the skin can reveal subtle, early findings in many febrile patients with immunocompromise. Ecthyma gangrenosum can be found in the axillae or on the perineum and usually signifies the presence of Pseudomonas or other Gram-negative bacteremia. A rectal examination in immunocompromised patients is mandatory to rule out perirectal disease.
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The physical examination should also attend to sites of barrier compromise (e.g., Foley’s catheter, indwelling line, wounds and prosthetic devices). Table 2 summarizes the important points in the physical examination apart from the other details.

**DIAGNOSTIC TESTS**

The work-up of the patient with fever and immunosuppression requires a high level of suspicion and involves a minimal battery of routine tests, augmented by aggressive study of potential sources of infection suggested by the clinical findings. Any site suspicious for infection after the history and physical examination should be imaged or cultured as soon as possible and liberal use of biopsy to establish a microbial diagnosis should be the rule. In the absence of localizing symptoms or signs, a minimal work-up includes urinalysis, chest radiograph, and blood and urine cultures (Table 3).

**BLOOD CULTURES**

Blood cultures should be drawn before antibiotic administration. Given the high rate of bacteraemia in the immunocompromised host, this simple test has a good chance of resulting in a microbial diagnosis and allowing targeted, maximally effective therapy. Attention to technique is critical to avoid contaminated specimens. Multiple cultures from separate sites, ideally taken as soon as the fever starts will be of great benefit in achieving the diagnostic goals. Two cultures drawn concurrently at separate sites expedite patient care and are adequate in most cases. Ten milliliters of blood inoculum per culture is ideal for adults and provides greater yields than cultures with smaller volume inoculum. Unfortunately, culture yields can be poor if outpatient antibiotics have been administered before the blood cultures are drawn in conjunction with central-line cultures to help resolve this issue.

In normal hosts, a positive *Staphylococcus epidermidis* culture is easy to attribute as a contaminant. In a patient with an underlying immune defect, the same culture must be taken much more seriously. If the isolate grows from more than one culture, true infection must be strongly considered.

**BIOPSIES**

Biopsies, including those obtained through bronchoscopy, can be invaluable in establishing a diagnosis. Open-lung biopsy is the best way to make a specific diagnosis in patients with pulmonary disease. Many invasive mycoses are diagnosed by biopsy as well. Liver biopsy can provide the microbial diagnosis of an otherwise nonspecific hepatitis.

**RADIO-IMAGING**

Chest radiographs can reveal findings that would otherwise go unappreciated clinically. Nonspecific findings on chest radiography are often present and usually do not affect initial management decisions, but they can prompt further diagnostic studies in patients who fail to respond to initial antibiotic treatment. Additional studies can prove fruitful if the initial evaluation is negative; however, using these tests as “screens” has a low yield. Chest CT can often clarify nonspecific findings on chest radiograph. Sometimes a presumptive diagnosis strong enough to allow narrowing of antimicrobial therapy can be made on the basis of classic findings on chest CT, such as with pulmonary aspergilllosis. CT/MRI results define the extent and location of disease and lead to changes in management. Abdominal CT and/or abdominal ultrasonography can reveal abdominal pathologies.

Basic blood work is also generally ordered. A complete blood count is necessary to determine the degree of granulocytopenia presence, if any. A complete blood count also provides a baseline measurement (a falling neutrophil count has a worse prognosis than a stable or rising count). Impaired renal function is not uncommon in this patient group, and liver function tests can be useful as well.

**DIFFERENTIAL DIAGNOSIS**

Table 4 provides a list of commonly seen immunocompromised patients by general immune defect and by pathogen groups likely to be responsible for infection.

**OTHER CAUSES OF IMMUNODEFICIENCY**


**GERIATRIC PATIENTS**

There is a physiologic decrease in immune function as people age. Additionally, older patients develop malignancies and develop diseases requiring treatment with immunosuppressive agents, putting them at even higher risk. Often, fever is the only finding
Typical causes

**Granulocytopenic**
- Cancer chemotherapy
- Marrow infiltration
- Marrow fibrosis
- Irradiation
- Drug reaction/allergies
- Sepsis
- Bone marrow transplant (First 3 weeks.)*

**Impaired cell-mediated immunity**
- Corticosteroid therapy
- Other drug-mediated immunosuppression (transplant/autoimmune)
- Acquired immunodeficiency syndrome (AIDS)
- Lymphoma
- Uremia
- Sarcoidosis
- Cancer chemotherapy

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<th>Deficit</th>
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<th>Pathogens</th>
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| Granulocytopenic | Cancer chemotherapy, Marrow infiltration, Marrow fibrosis, Irradiation, Drug reaction/allergies, Sepsis, Bone marrow transplant (First 3 weeks.) | **Bacteria**
  - *Staphylococcus* spp. *Escherichia coli, Klebsiella* spp.**
  - *Yeast/Fungi*
  - *Pseudomonas* spp., *Candida* spp., *Cryptococcus neoformans*, *Aspergillus* spp., *Mucormycosis*
| Impaired cell-mediated immunity | Corticosteroid therapy, Other drug-mediated immunosuppression (transplant/autoimmune), Acquired immunodeficiency syndrome (AIDS), Lymphoma, Uremia, Sarcoidosis, Cancer chemotherapy | **Bacteria**
  - *Listeria, Salmonella, Legionella, tubercle bacillus (TB), Atypical mycobacteria*
  - **Viruses**
  - *Cytomegalovirus (CMV), herpes simplex viruses (HSV), herpes zoster virus (HZV), Epstein-Barr virus*
  - **Fungi/Yeast/Mycoses**
  - *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Coccidioides immitis, Histoplasma capsulatum*
  - **Protozoan**
  - *Cryptosporidium* spp., *Pneumocystis carinii, Toxoplasmosis gondii*
  - **Helminth**
  - *Strongyloides stercoralis, Actinomycetes, Nocardia* |

::TABLE 4 General immune defect and pathogen groups

*Infection in febrile neutropenics is microbiologically confirmed in 25–30% of cases and clinically documented in 30–40%. Fever in the absence of identifiable disease is common and can represent serious or life-threatening infection, especially bacteraemia or sepsis.*

**The Patient with Granulocytopenia**
Granulocytopenia can be caused by decreased cell production, increased peripheral destruction or peripheral pooling. The commonest cause of granulocytopenia is cancer chemotherapy. Granulocyte depletion, however, is the greatest risk factor for infection and defines the clinical picture in these patients. Granulocytopenia is associated with a marked increase in serious infections, most often bacterial. The level of neutropenia in the emergency department (ED) patient with fever determines a great deal of the risk of life-threatening infection. Less than 3,000 cells/mm$^3$ defines neutropenia, but it is not until counts fall to 1,000 cell/mm$^3$ that the incidence of infection starts to increase. At counts of 500 cells/mm$^3$, there is a dramatic increase in the incidence of severe infections: most authorities recommend the initiation of empiric, parenteral, broad-spectrum antibiotics at levels of 500 cells/mm$^3$ or less. Some authors recommend initiating therapy at counts of 1,000 cells/mm$^3$ or under, whereas others use an absolute count of 200 cells/mm$^3$ or less. In addition to the absolute counts, the rate of decline in the count and the time table of neutropenia can be factors as well. Initial infections are usually bacterial; after about 2 weeks of neutropenia, the incidence of *Aspergillus* and *Candida* increase. Prolonged neutropenia is associated with infection rates that reach 100% at 14 weeks and decrease in neutrophils results in a decrease in the inflammatory response, potentially masking the symptoms and signs clinically associated with infections. The presence of pharmacologic agents (e.g. pain medications with acetaminophen, non-steroidal anti-inflammatory drugs, and steroids) that further reduce the inflammatory/febrile response can add to the camouflage. Age can be another confounding factor, because elderly patients exhibit a decrease in the immune/inflammatory reaction compared with younger hosts.*

**THE PATIENT WITH GRANULOCYTOPENIA**

The patient with granulocytopenia can exhibit a decrease in the immune/inflammatory reaction compared with younger hosts.

Infection in febrile neutropenics is microbiologically confirmed in 25–30% of cases and clinically documented in 30–40%. Fever in the absence of identifiable disease is common and can represent serious or life-threatening infection, especially bacteraemia or sepsis. The difference between aggressive infection and more benign disease or noninfectious fever can be difficult to determine. Withholding antibiotics in a febrile, neutropenic patient clearly leads to an increase in mortality and morbidity. In most cases, the pathogen is endogenous. The most commonly identified sites of infection among neutropenics are the mouth and pharynx, the lower respiratory tract, skin, soft tissue and intravascular catheters, perianal region, urinary tract, nose and sinuses and the GI tract.

Isolated fever in the immunocompromised host can indicate bacteraemia and can signal the onset of Gram-negative sepsis. Gram-negative bacteraemia carries a worse prognosis than other infections in the neutropenic host and can be a rapidly progressive, fatal infection. The mortality rate for Gram-negative sepsis involving *Pseudomonas aeruginosa* ranges from 33% to 75%.

**EMPIRICAL ANTIBIOTIC THERAPY IN INTENSIVE CARE UNITS**

Studies in the early 1970s established that granulocytopenic patients with fever had an increase in mortality if antibiotic therapy was delayed due to delayed microbial culture reports. Over time, with the early initiation of empiric antibiotic coverage, the mortality rate for Gram-negative bacteraemia in neutropenic patients has fallen from 90% to 10%. Once the problem of infection in the immunocompromised host is recognized and cultures are collected, initial antibiotics should be given. Administration of an initial regimen in the intensive care units (ICU) is critical because patients can suffer significantly. The issue of choosing an appropriate antibacterial regimen is complex and is based on the particular clinical situation. Fever without localizing findings mandates the broadest spectrum of coverage. There should be no delay in administration of the drug(s), and protocols should be specifically designed around local patterns of prevalence and resistance. Therapy with an aminoglycoside...
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combined with either an antipseudomonal beta-lactam penicillin or a third generation cephalosporin offers broad-spectrum coverage with rapid bactericidal activity, antipseudomonal activity and synergism. With the development of newer antibiotics (especially third-generation cephalosporins, carbapenems), acceptance of initial monotherapy in certain situations is evolving.

Modifications to this basic initial regimen are: anti-anaerobic coverage (e.g. clindamycin, metronidazole) is added in cases that are suspect, such as perirectal disease, necrotizing gingivitis or intra-abdominal infection. Vancomycin is considered in a patient with an infected intravenous line or in the presence of possible methicillin-resistant *Staphylococcus aureus* (MRSA). Antifungal agents can be used initially if severe local and/or systemic fungal infections or if mucormycosis is suspected. Antiviral agents can be indicated as well in the presence of herpes virus infection.

**COMMON PATHOGENS**

Nationally, centers are noting a change in the microbiology of febrile neutropenic episodes. The incidence of Gram-negative disease, and especially *P. aeruginosa*, is decreasing, while infections due to Gram-positive cocci are increasing in frequency. The rate of isolation in blood cultures of viridans streptococci especially has seen a documented increase over time. In proven Gram-negative disease, *Escherichia coli* and *Klebsiella pneumoniae* remain the most commonly isolated pathogens. The presence of fungal disease is probably under-recognized, especially in certain malignancies such as leukemia and lymphoma.

**CONFUSING PATIENTS: OCCULT IMMUNOCOMPROMISE AND INFECTION WITHOUT FEVER**

Noninfectious sources of fever are present in patient populations with occult immunocompromise and life-threatening infection can be present in the absence of fever. Differentiating between “sick” and “not sick” in an immunocompromised patient with fever is treacherous. The latter case, with more subtle manifestations of significant occult infection, can become the source of diagnostic confusion. A decrease in level of functioning, mild confusion, or isolated tachycardia can be the only findings, and the patient’s presentation might appear quite benign. In immunocompromised patients, infectious disease is a main source of morbidity and mortality and is a potential explanation for any change of the patient’s status quo.

**CONCLUSION**

A subset of patients seen in the ICU has impaired immune systems. Fever in the immunocompromised host may represent a life-threatening medical emergency. Prompt recognition of the underlying host defect and an understanding of the immunophysiology of that defect is key to a focused search for potential sites of infection and a differential diagnosis of potential pathogens. Fever may be the sole finding; the absence of other classic symptoms and signs of infection should not prevent the emergency physician responsible, from evaluating these patients. A high degree of suspicion should be maintained, and atypical history and physical examination details should be pursued aggressively. Rapid laboratory and imaging work-up is indicated and admission to the hospital is most often necessary. Prompt administration of appropriate broad-spectrum empiric antibiotics decrease morbidity and mortality.

**REFERENCES**