Sepsis in immunocompromised hosts

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Over the past 20–30 years there has been a dramatic increase in the number of people living with immunosuppression. Cancer chemotherapy and the treatment of haematological disease transiently put people at risk, while the immunosuppression required for solid organ transplants and for immune-mediated diseases, such as systemic lupus erythematosus, is more prolonged. In addition to these iatrogenic causes of impaired immunity, there is an increasing burden of HIV infection and better survival of individuals with primary immunodeficiency. This article will attempt to outline the defects in host defences in some of these groups, and show how the presentation, diagnosis and management of sepsis may differ from that seen in normal hosts.

The abnormal hosts mentioned above fail to respond appropriately to infecting pathogens and opportunistic organisms because of defects in one or more of the components of the immune system:

- neutropenia and other phagocytic defects
- poor cellular immune function
- humoral immune dysfunction, including complement defects
- functional or anatomic asplenia

Patients without a functioning spleen

The spleen is an important organ in the lymphatic system, principally involved in clearing poorly opsonised particles from the circulation. It also has an important role in B lymphocyte responses to polysaccharide antigens. In addition, it produces properdin, which is involved in complement activation, and tuftsin, which may be involved in opsonisation.

In practice, the major problem for those without a spleen is the risk of overwhelming infection with encapsulated bacteria, particularly the pneumococcus (*Streptococcus pneumoniae*). Other bacteria that may cause problems are *Haemophilus influenzae* and *Neisseria meningitidis*, and the unusual organism *Capnocytophaga canimorsus* (formerly called DF2). Although all have been reported as causing sepsis in asplenic individuals, most of the data relate to serious pneumococcal infection. The lifetime risk of sepsis is estimated to be around 5%, but it is clear that the risk is higher in children than in adults and is probably greatest in the first two years following splenectomy.

Overwhelming infection in the asplenic patient may start with a prodrome of vague malaise and sore throat, followed soon after by rigors and fever. Within 24 hours the patient develops shock, generally with disseminated intravascular coagulation and acute respiratory distress. There is usually no obvious focus for the infection. Management relies on early recognition, the prompt institution of broad spectrum antibiotics that will cover the pneumococcus, and intensive care support. Pneumococcal vaccine and prophylactic antibiotics are often advised to prevent such sepsis, but there is no evidence that they do so.

There are anecdotal reports of asplenic patients developing severe infection with a tick-borne parasite, babesia, that is endemic along the north-eastern seaboard of the USA and in northern Europe. Patients develop fever, rigors and thrombocytopenia. Babesia species are red cell parasites and may be mistaken for malarial parasites. However, the tetrad appearance on blood films is characteristic. Management is with clindamycin and quinine, although a new agent, atovaquone, may be useful. Splenectomised patients may also require exchange transfusion.

Malignancy

Chemotherapy for malignant disease, especially haematological malignancy, almost invariably leads to a period of neutropenia (<500 neutrophils/mm$^3$). Intensive induction therapy in leukaemia may lead to severe neutropenia for 2–3 weeks, but less intensive chemotherapy may cause neutropenia for only 10–14 days. The risk of infection increases with the duration of neutropenia but may occur in up to 80% of those receiving intensive treatment. In addition to the numerical defect in neutrophils, there are often subtle phagocytic defects which, with poor haematopoiesis in haematological malignancy, further increase the infection risk. There may also be dysfunction in the humoral and cellular components of the immune system depending on the underlying disease.

The most important infective risk in these patients is Gram-negative septicemia caused by endogenous organisms. These bacteria are usually of gastrointestinal origin; because of the mucositis induced by the chemotherapy, they are ‘translocated’ from the gut lumen across the mucosa to enter the circulation. Patients develop fever and
may become hypotensive, usually without an obvious focus of infection. A variety of organisms can cause sepsis in this way but the highest attributable mortality is associated with *Pseudomonas aeruginosa*. In recent years, there has been an increase in the prophylactic use of oral quinolone antibiotics. While this can reduce the incidence of Gram-negative sepsis, the pattern of infection has been shifted in the direction of Gram-positive organisms. In many centres now, neutropenic sepsis is due to *Staphylococcus aureus*, coagulase-negative staphylococci and streptococci derived from the skin or the oropharynx. The presence of indwelling vascular catheters also increases the risk of sepsis.

Neutropenic patients are also at increased risk of lower respiratory tract infections. Inpatients in particular rapidly become colonised with Gram-negative organisms in the oropharynx and upper gastrointestinal tract. Aspiration of pharyngeal secretions or gastric contents can lead to pneumonia. When sepsis occurs in this setting, there may be obvious respiratory symptoms and signs, such as increased respiratory rate and crackles in the chest.

The management of neutropenic sepsis relies on the prompt institution of broad spectrum antibiotics, usually including an anti-pseudomonal beta-lactam and an aminoglycoside. Antibiotics such as vancomycin which are active against Gram-positive organisms may be added if the fever does not settle promptly or if these organisms are known to be a problem on the unit. Although many episodes of neutropenic sepsis may not be associated with positive blood culture, studies have shown that empirical therapy reduces complications. The duration of therapy is less clear, but treatment should continue until the neutrophil count recovers and the patient has remained afebrile for a few days. Persistent fever in the face of antibiotics may indicate systemic fungal infection, a rare cause of sepsis in the normal host.

Systemic fungal infection may occur in up to a third of neutropenic patients, with a fever unresponsive to antibiotics, and is an increasing cause of mortality in this group. The main pathogens are *Candida* spp. and *Aspergillus* spp., although rarer fungi such as *Fusarium* spp. and *Trichosporon* spp. are increasingly reported. Many candida infections represent spread from a site of colonisation, such as the gut, a vascular catheter or the urinary tract. There is usually fungaemia but this can be difficult to detect. Candida rarely leads to pneumonia, but may involve the liver, spleen and kidneys. With the increasing use of prophylactic oral imidazole antifungal agents such as fluconazole, there has been an increase in non-albicans *Candida* spp., such as *Candida glabrata* and *Candida krusei* which are relatively or absolutely imidazole-resistant.

Aspergillus infections usually follow the inhalation of spores from the environment, the risk of this being increased if there are building works nearby that increase the spread of dust. Sepsis due to aspergillus in these patients usually has a respiratory focus, the diagnosis of which can be facilitated by early high-resolution computed tomography scanning of the lungs. Sometimes patients have respiratory symptoms and signs such as chest pain, haemoptysis or a pleural rub. Cerebral aspergillus infections are almost invariably fatal.

The increased risk of fungal infection in neutropenia has led to the empirical use of antifungal agents in febrile episodes not responding to antibiotics. Intravenous amphotericin B has been the gold standard of treatment, but recent studies have shown that liposomal amphotericin B is equally efficacious and associated with less toxicity. Newer imidazoles such as voriconazole may also have a role, but there are no data yet to change practice.

**Bone marrow transplantation**

Bone marrow transplantation (BMT) is associated with prolonged neutropenia and an increased risk of bacterial infection in the first 100 days after transplantation. More recently, traditional BMT has been replaced by peripheral blood stem cell (PBSC) transplantation which allows earlier engraftment and, with the addition of growth factors, reduces the period of neutropenia. However, there is a higher risk of graft versus host disease (GVHD) because of the greater proportion of lymphocytes in PBSC grafts. The risk of infection is increased if GVHD occurs and requires immunosuppressive therapy. The risk is also greater in allogeneic transplants than in autologous grafts. Although Gram-negative infections are still a risk, infections with coagulase-negative staphylococci are increasingly common, probably secondary to indwelling vascular catheters. The cellular immune defects associated with BMT increase the risk of cytomegalovirus (CMV) infections. These can present as simple fevers, but may cause severe sepsis and pneumonia. Strategies to prevent CMV disease in the early post-transplant period have shifted the emphasis towards fungal infection in this period. Candida sepsis and infection with *Aspergillus* spp. are now more likely as causes of death in the first 100 days after BMT. Routine antifungal prophylaxis has reduced the incidence of *Candida albicans* but has not affected aspergillus infections. The clinical presentation of such infections following BMT or PBSC transplants is similar to that seen in haematological oncology patients.

Effective prophylaxis and treatment in the early post-transplant period has led to a higher incidence of infection in the late (>100 days) period after engraftment. Bacterial infections, including pneumonia, have been noted and CMV is presenting as a late cause of sepsis. Aspergillus infection can also appear late. All these late infections are increasingly likely if GVHD has occurred, and may persist in the presence of chronic GVHD. Those free of GVHD usually have a sufficiently reconstituted immune system by about 18 months post-transplant for the risk of infection to recede.

**Solid organ transplantation**

In the early post-transplant period, recipients of solid organs are most at risk of bacterial sepsis. Urinary tract infection or infected wounds are com-
mon sources of sepsis, as are indwelling lines. Deterioration can be rapid, so empirical antibiotic therapy is justified in this setting. Therapy should cover Gram-negative organisms (the most common causative agents) and common Gram-positive bacteria associated with line sepsis. Two unusual organisms may cause sepsis in organ transplant recipients:

- **Listeria monocytogenes** may cause bacteraemia or pneumonia but can also present as a meningoencephalitis.
- **Nocardia** infections are usually disseminated, but often present with lung infiltrates or as cerebral abscesses.

Co-trimoxazole prophylaxis probably reduces the risk of these two rare infections.

Fungal infections also occur in these patients and are most common in liver transplants.

Herpes virus infections, particularly CMV, may be relatively mild and present as a simple fever but can be disseminated and associated with severe symptoms of sepsis. The risk is greater if episodes of graft rejection require treatment with increased immunosuppression. Antiviral prophylaxis and empirical therapy based on surveillance screening for CMV viraemia can reduce the risk of severe disease.

**Connective tissue diseases**

The so-called connective tissue – or immune-mediated – diseases can have a wide spectrum of immunosuppression due either to the underlying disease, such as SLE, or to the drugs used for treatment, such as corticosteroids, cyclophosphamide and azathioprine. The risk of infection is usually lower than for solid organ transplants but the types of infection are not dissimilar. Many present with sepsis in the setting of new lung infiltrates on chest radiograph. Although bacterial infections are common, the differential diagnosis includes viruses, mycobacteria and fungi.

**HIV infection**

Although the management of HIV has been dramatically altered by the use of highly active antiretroviral therapy (HAART), new patients continue to present with infection. *Pneumocystis carinii* pneumonia (PCP) still occurs; although it usually presents insidiously with cough and breathlessness, it can occasionally present acutely with fever and signs of sepsis when the diagnosis may not be readily apparent. Systemic fungal infections may also present with a sepsis syndrome, most commonly cryptococcosis. These patients often have lung infiltrates, many are fungaemic and most have meningitis. Optimal management includes intravenous amphotericin and 5-flucytosine, although imidazoles such as fluconazole may be used for mild cases. Other geographically restricted fungal infections, such as histoplasmosis, penicilliosis and coccidioidomycosis may present in a similar manner.

Opportunist infections, such as those above, are not the only causes of sepsis in HIV. In addition to cellular immune defects, immunoglobulin synthesis and macrophages are dysfunctional and people with HIV are prone to infection with encapsulated bacteria, especially pneumococci. Pneumococcal pneumonia and bacteraemia are increased in HIV and may be the earliest features of immunosuppression. There is also an increased risk of non-typoidal salmonella bacteraemia which may recur following appropriate antimicrobial therapy. More recently, it has been recognised that pseudomonas bacteraemia is increasing in HIV infection, with many cases apparently community-acquired and lacking the risk factors normally associated with nosocomial pseudomonal infections. The occurrence of such bacteraemias in relatively young patients should prompt the consideration of HIV testing.

**Conclusions**

The immunocompromised patient, like any other host, may present with serious bacterial sepsis and can be managed along similar lines. However, the specific host defects vary with the type of immunodeficiency and lead to increased risks of other, non-bacterial infections. The need for empirical therapy in this setting is recognised, but broader diagnostic thinking and more extensive investigations are required to focus treatment and deal specifically with certain viruses and fungi that are the main causes of morbidity and mortality in these patients. Early consultation with an expert in infection can be helpful, and there is no substitute for continued clinical vigilance in such cases. There is an urgent need for better diagnostic tests and treatments for viruses and fungi, such as aspergillosis.

**References**

Mechanisms and detection of bacteraemia

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Bacteraemia refers to the presence of viable bacteria in the bloodstream. This may be transient and of little clinical significance; for example, we all experience transient bacteraemia when brushing our teeth. The consequences of bacteraemia may, however, be severe, leading to focal infection (osteomyelitis, endocarditis) or systemic illness (severe sepsis, shock and death). Thus, an appreciation of the mechanisms underlying bacteraemia is critical in understanding the pathogenesis of many infections.

Mechanisms underlying bacteraemia

To cause sustained bacteraemia, an organism must be able to penetrate host defences and then avoid the immune response, particularly complement-mediated killing and opsonophagocytosis.

Penetration of mucosal surfaces

Cutaneous and mucosal surfaces protect against continual exposure to environmental organisms. Bacteria that colonise or invade these sites may in certain circumstances lead to significant local disease and/or bacteraemia (Fig 1). In order to cause disease in a host with intact mucosal barriers an organism must possess both specific surface adhesion molecules to allow adherence to the epithelial surface and a mechanism for penetration. Many strains of Escherichia coli are unable to adhere to urinary epithelium. E. coli cultured from patients with urinary tract infection, however, have surface pili with receptors that bind to uroepithelium. This general principle applies to many other pathogens, including parasites, fungi and viruses: for example, rhinoviruses that cause the common cold have a surface protein that binds to intercellular adhesion molecule (ICAM)-1 on nasal epithelium.

Once adherent to an epithelial surface, many bacteria remain as colonising organisms and do not invade. Some pathogens have the ability to penetrate between epithelial cells or may be phagocytosed and cross directly through epithelia. This process may be facilitated by epithelial damage permitting traffic of colonising bacteria and subsequent invasion and possible bacteraemia. Damage to the epithelium may be direct, such as trauma or toxins, or it may be caused by another organism. This combination of factors is well

Key Points

- Bacteraemia is the result of bacterial invasion through host epithelia
- Epithelial damage increases the risk of bacteraemia
- Host defences destroy or clear most bacteria from the bloodstream
- Pathogenic bacteria have cell surface features that avoid serum killing and opsonophagocytosis
- Blood cultures need to be taken correctly to optimise yield
- Rapid diagnostic techniques have the potential to improve empirical antibiotic therapy and clinical outcome