



University
of Glasgow

Quasim, T. (2010) *Immunosuppressed patients*. In: Gao Smith, F. and Yeung, J. (eds.) *Core Topics in Critical Care Medicine*. Cambridge University Press, Cambridge, UK, pp. 116-123. ISBN 9780521897747

<http://eprints.gla.ac.uk/5280/>

Deposited on: 24 August 2010

IMMUNOSUPPRESSED PATIENTS

The immune system is a highly complex physiological cascade that protects the body from 'foreign' pathogens. A defect at any point in this system can lead to both an increase in the incidence and an increase in the severity of infections. An immunosuppressed patient is unable to mount the normal, co-ordinated immune response to trauma and infection. The aetiology of the immune defects can be divided into primary (congenital) or secondary (acquired) disorders.

Figure 1

Improvements in the treatment of immune disorders have increased the number of referrals and admissions to the ICU. Patients may present because of their primary illness or a new pathology which is complicated by their immunosuppressant therapy, for example a perforated viscus.

Whilst chronic illnesses such as diabetes mellitus can predispose to a degree of immunosuppression, the groups that will be discussed in this chapter include:

- Patients with cancer or haematological malignancies.
- Recipients of solid organ transplants.

- Patients with HIV/AIDS.
- Patients with asplenia or functional hyposplenism.

GENERAL CONSIDERATIONS

Infection

Respiratory failure or sepsis are the commonest reasons for immunosuppressed patients to require ICU admission. The exceptions to this are patients post solid organ transplant.

Whilst there is no specific therapy for the immunosuppressed patient, the principles outlined in the surviving sepsis guideline (www.survivingsepsis.org) should be followed.

Immunosuppressed patients may be critically ill yet display little in the way of signs or symptoms. This key point means a detailed history, together with a high index of clinical suspicion is vital. Knowing the aetiology of the immunosuppression can provide invaluable clues as to the likely pathogen causing the infection. For example, neutropenia confers susceptibility to bacteraemia whilst long-term steroids (>15-20mg/day) increase host susceptibility to viruses, fungi and parasites as well as bacteria.

The infections they sustain are often of greater severity and may have a rapid progression. The prior use of prophylactic and therapeutic antibiotics may mean that the potential for resistant organisms is increased. Microbiological diagnosis should be pursued and early liaison with microbiology is vital to ensure broad spectrum cover. Invasive procedures such as CT guided needle biopsy, broncho-alveolar lavage and transbronchial biopsy may be required to obtain a sample of sputum or tissue when a respiratory source is suspected. These investigations can lead to further complications, especially if patients

are requiring high inspired concentrations of oxygen and high PEEP levels. When infection is suspected, a reduction in the dose of immunosuppressant therapy may be equally as important as commencing antibiotics to allow an adequate host response.

Particular risk factors for developing infection include:

- Neutropenia. An absolute neutrophil count below $0.5 \times 10^9/L$ or those in whom the neutrophil count is falling rapidly.
- New leukaemia or lymphoma.
- Recent haematopoietic stem cell transplant (HSCT) recipients and allogeneic HSCT recipients with significant degrees of graft versus host disease (GvHD).
- Recent infections especially due to cytomegalovirus (CMV), or with known colonisation with fungi or resistant bacteria.
- Co morbid illnesses requiring hospitalisation.
- The use of peripheral and central venous catheters and urinary catheters.

Respiratory failure

Respiratory failure can result from multiple simultaneous pulmonary processes, both infectious and non infectious. Non infectious complications include thromboembolism, tumour, radiation pneumonitis, atelectasis, pulmonary oedema, drug allergy or toxicity and pulmonary haemorrhage.

In addition to the usual 'common' pathogens, these patients are at increased risk of opportunistic infections and reactivation of latent infections such as toxoplasmosis, herpes viral infections or tuberculosis.

The common pathogens include:

Bacteria: *Streptococcus pneumoniae*,

Haemophilus Influenzae

Mycoplasma

Legionella

Viruses: CMV is the most common virus of concern, especially in transplant recipients and is often difficult to distinguish from non-invasive viral infection. Its incidence is related to the intensity of the immunosuppressant therapy and usually occurs in the first few months post transplant. In patients not receiving prophylaxis *pneumocystis jiroveci/carinii* (PCP) is associated with CMV infection.

Fungi: *Cryptococcus neoformans*

Aspergillus. Invasive aspergillosis is increasing in incidence and is associated with a high mortality.

Pneumocystis jiroveci/carinii is not uncommon in patients receiving steroids as part of a chemotherapeutic or maintenance regimen.

SPECIAL CONSIDERATIONS

Patients with cancer and haematological malignancies

As a consequence of both the primary illness and its treatment, patients with malignancies are prone to episodes of neutropenia. The presence of a fever in a neutropenic patient is to be taken seriously. It is often the only sign of a bacteraemia. Factors contributing to the pathogenesis of infection include the

direct effects of chemotherapy on mucosal barriers and the immune deficits related to the underlying malignancy.

The likelihood of there being an underlying bacterial cause is greatest when the neutrophil count is $< 1 \times 10^9/L$. The high mortality associated with gram negative organisms has led to the use of prophylactic antibiotics; however gram positive organisms are now common isolates, especially in patients with long term vascular access catheters. Validated regimens that are commonly used include antipseudomonal penicillin and aminoglycoside or a single agent regimen such as a third generation cephalosporin or a penem. As these agents give relatively poor gram positive cover consideration should be given to introducing vancomycin.

After 5 days, if the patient has continued fever but is clinically stable and has resolving neutropenia, the initial antibiotic regimen can be continued. However, if there is evidence of progressive disease then consideration should be given to changing or adding further antibiotics. Treatment should continue for at least 1 week and ideally until the neutrophil count is $> 0.5 \times 10^9/L$ or 14 days have elapsed.

A high, swinging pyrexia in the absence of a readily identifiable focus should raise the possibility of a deep fungal infection. Fungi are common pathogens and the risk of a fungaemia increases with the duration and severity of neutropenia, prolonged antibiotic use and the number of chemotherapy cycles. Consideration should be given to adding an antifungal agent if there is a persistent temperature after 72 hours.

Unique considerations post haematopoietic stem cell transplant (HSCT)

HSTC can be either autologous (derived from the patient) or allogenic (from a donor). Despite advances, the success of HSCT remains limited by severe complications that are related to the toxicity of the conditioning regimen required prior to allogenic HSCT, immunosuppression and GvHD disease. Complications usually occur in the first 100 days post HSCT. The presence of more than 1 organ failure, regardless of organ type increases the mortality in this patient population. Mortality rates of 75-85% have been quoted in patients requiring mechanical ventilation.

HSCT recipients are prone to unique pulmonary complications.

- **Engraftment syndrome.** Occurs within 96 hours of engraftment and can arise in autologous and allogenic recipients. It can cause fever, erythematous rash, diarrhoea, renal impairment and multiorgan failure. The syndrome coincides with neutrophil recovery and the treatment is supportive.
- **Diffuse alveolar haemorrhage.** Injury to the endothelial cells of small blood vessels and thrombotic microangiopathy due to high dose chemotherapy can cause this condition. Symptoms include progressive dyspnoea, cough, fever and hypoxia. The treatment is supportive, however the prognosis is poor with most patients dying of sepsis and multiorgan failure rather than respiratory failure.
- **Idiopathic pneumonia syndrome** is a syndrome of diffuse lung injury that develops post HSCT where an infectious cause is not found.
- **Bronchiolitis Obliterans Organising Pneumonia (BOOP)** is related to GvHD and usually responds to steroids. It has a good prognosis and doesn't usually require critical care services.

Infection and complications in solid organ transplant recipients

Despite rigorous screening, transmission of infection from the donor organ can occur. Some donors may have active infection at the time of procurement. Fever, bacteraemia or even mycotic aneurysms at anastomotic sites can occur in the recipients. Proof of adequate treatment of such infections must be established prior to organ donation. Other infections may not be apparent, or be accelerated in the recipient, after commencing immunosuppressant therapy.

Viral infections, especially CMV and Epstein-Barr virus (EBV), can cause particular problems in the transplant recipient. The greatest risk is seen in the seronegative recipient and seropositive donor.

Late, latent infections, including TB, can also activate many years after transplantation.

Not surprisingly, lung transplant patients have a higher risk of developing pulmonary infection than other solid organ transplant recipients. Reasons for this include:

- An extended intubation period leading to colonisation of the lower respiratory tract.
- Trauma sustained by the lung during transplantation.
- Mechanical factors such as decreased ciliary action and reduced cough reflex.

Complications post organ transplant can be divided into 3 timelines:-

Up to 6 weeks post transplant:

Infections can be derived from the donor or recipient; in addition there is the potential for the usual post-operative infectious complications and hospital acquired infections. In these patients the effects of immunosuppression are not often evident unless they have been receiving immunosuppressant therapy pre-operatively.

1-6 months post transplant:

It is in this time period that patients are at most risk of developing opportunistic infections, although problems from the perioperative period can persist. The major infections due to opportunistic pathogens include PCP, latent infections, viral pathogens and TB. Viruses can also cause direct clinical effects such as fever and neutropenia (CMV), pneumonitis (respiratory viruses), hepatitis (HBV, HCV) etc.

Graft rejection is thought to be mediated by proinflammatory cytokine release and may require an increase in immunosuppressant therapy leading to an increased risk of opportunistic infection.

After 6 months:

At this time most patients are receiving stable and reduced levels of immunosuppression and are prone to the usual community acquired pathogens.

Common Immunosuppressant Drugs

- **Steroids** limit cytokine and chemokine synthesis, induce apoptosis and limit acquired immune responses predominantly by attenuating T cell actions. The risk of infection is dose and time related. The highest risk occurs with doses >0.5 mg/kg/day of prednisolone or equivalent agents, or a cumulative total dose of >700 mg. The risk of sepsis is

related to diminished phagocytosis and killing of bacterial and fungal pathogens. Long term therapy can cause defects in cell mediated immunity and cause opportunistic infections.

- **Cytoreductive agents** induce dose related reductions in rapidly dividing cell lines and causing neutropenia and mucositis. When used in lower doses as an immune modulator, methotrexate has been associated with opportunistic infections.
- **Immunophilin binding agents** are used primarily in transplantation, limiting cytotoxic T-lymphocyte expansion and graft rejection. This is achieved by attenuating the signalling system for IL-2 production by calcineurin inhibition (cyclosporine and tacrolimus) or inhibition of lymphocyte mRNA transplanted and IL-2 synthesis (sirolimus or rapamycin). As they primarily affect T cells the risk of bacterial and fungal infection is quite low.
- **Mycophenolate** specifically inhibits the de novo pathway of purine synthesis in B and T cells. There is specific inhibition of lymphocyte clonal expansion on exposure to appropriate antigens. The risk of sepsis is reduced but its use has been associated with opportunistic, intracellular viral infections, specifically CMV disease and EBV associated with lymphoproliferative disorder.
- **Anti-TNF agents** inhibit the host innate and acquired immune responses to microbial pathogens. Anti-TNF treatment (infliximab, etanercept) is used in severe RA and Crohn's and has been associated with severe, disseminated infection.

HIV AND AIDS

With the advent of highly active antiretroviral therapy (HAART), the prognosis of patients with HIV and AIDS has improved enormously. Compared with other ICU groups with similar severity of illness, HIV patients no longer have a worse outcome. Patients are increasingly admitted to the ICU with HIV as a co morbid disease rather than as the primary admission reason.

HIV and its therapy can cause multisystem problems:

Respiratory failure still remains the commonest cause for ICU admission.

This can be due to varied pathologies including, PCP, TB or other mycobacterial disease. Patients with PCP and a pneumothorax requiring mechanical ventilation still have a mortality approaching 100%.

Cardiac disease can occur in these patients as HAART is associated with atherogenesis and metabolic complications such insulin resistance and diabetes. It is also known that HIV patients who undergo percutaneous coronary intervention have higher restenosis rates than those who do not.

End stage liver disease secondary to viral hepatitis can cause significant morbidity and mortality. Patients receiving concurrent HIV and HBV treatment should ideally continue both therapies as severe relapses of hepatitis B may occur if it is stopped.

Renal impairment is a frequent cause of mortality and morbidity. Treatment options include renal replacement therapy +/- transplantation. The HIV infection itself appears to be the cause of HIV associated nephropathy and in this clinical scenario HAART can slow disease progression.

Immunologic reconstitution can occur when established HAART therapy reduces the viral load and causes a general increase in pro-inflammatory

mediators and effects. A number of disorders are related to this and are collectively termed the immune reconstitution inflammatory syndrome (IRIS).

With the addition of steroids HAART can often be continued in this situation.

Co-infection of HIV and HCV has major mortality effects. HCV related deaths are more common after improved HIV treatment with HAART. It appears that impaired cellular immunity from HIV leads to accelerated HCV reproduction. Conversely HCV has also accelerated the progression of HIV disease.

Antiretroviral therapy in ICU

HAART generally consists of 2 nucleoside reverse transcriptase inhibitors (NRTI's) and either 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) or 1 or 2 protease inhibitors (PI's).

Table 1

General principles for deciding on whether to commence HAART in the ICU are as follows.

- If the patient is not on treatment but admitted with an AIDS related illness, consider commencing antiretrovirals.
- If not admitted with an AIDS related illness this decision can probably be deferred. If the CD4 count is less than $200/\text{mm}^3$ and the patient is having a prolonged ICU stay consider treatment, as this increases risk of an opportunistic infection.

The main problems encountered with HAART in the ICU are:

- **CONTINUATION OF DRUG THERAPY**

Achieving adequate plasma levels in those patients that cannot swallow may be problematic. If an oral solution is not available, tablets or capsules have to be crushed. If the enteral route cannot be utilised,

few drugs have an intravenous formulation. Potential problems, therefore include sub therapeutic drug levels and drug resistance, or supra therapeutic drug levels and adverse effects. In addition, discontinuing HAART in the ICU is undesirable, as it may also lead to the selection of a drug resistant virus.

- PHARMACOKINETICS AND PHARMACODYNAMICS

Commonly used ICU interventions such as enteral feeding, proton pump and H₂ antagonists can affect the pharmacokinetics and pharmacodynamics of antiretrovirals.

Renal insufficiency decreases the clearance of most nucleoside reverse transcriptase inhibitors (NRTI's) therefore these patients cannot use most of the fixed dose NRTI combinations. Hepatic impairment will also decrease the metabolism of many protease inhibitors and NNRTI's.

- DRUG INTERACTIONS

There are many interactions between antiretrovirals and common ICU drugs; protease inhibitors are particularly vulnerable as they are metabolised by the cytochrome P450 system. Commonly used drugs that can interact with HAART include:

Midazolam: Interacts with most PI's and NNTRI's leading to increased sedative effects.

Amiodarone, Diltiazem and Nifedipine: Interact with some PI's to cause increased cardiac effects.

- TOXICITY

HAART has decreased the incidence of AIDS related illnesses however it has been implicated in rare life threatening conditions such as Stevens Johnston syndrome. Other toxic side-effects include pancreatitis, lipodystrophy, insulin resistance and hyperlipidaemia. NNRTI's can cause a fatal lactic acidosis by disrupting mitochondrial DNA replication by selective inhibition of DNA polymerase- γ . This can cause hepatic steatosis, lactic acidosis or mitochondrial myopathy. Treatment involves stopping the drug.

ASPLENIA

Splenic macrophages have an important filtering and phagocytic role in removing bacteria and parasitized red cells from the circulation. Life threatening infection is a major long term risk post splenectomy. Most serious infections are due to encapsulated bacteria.

With the advent of vaccinations, this risk can be minimised and national guidelines are in place to offer prophylaxis to all patients who have either undergone a surgical splenectomy or have functional hyposplenism (sickle cell, thalassaemia major, lymphoproliferative disorders, bone marrow transplant).

Vaccines against pneumococcus, meningococcus and Haemophilus influenza B should be administered 2 weeks prior to an elective splenectomy or as soon as possible after surgery and certainly prior to hospital discharge. These patients are also offered the flu vaccine on a yearly basis.

Lifelong antibiotics should be offered to all patients, however, the first 2 years post splenectomy appears especially important. The antibiotic prophylaxis of

choice is oral phenoxymethylpenicillin 250-500mg twice daily or erythromycin if the patient is penicillin allergic.

Keypoints

- Immunosuppressed patients may be critically unwell, yet display minimal clinical signs and symptoms.
- In addition to the usual pathogenic organisms, these patients are prone to opportunistic infections and reactivation of latent infections. Knowing the aetiology of the immunosuppression can help target therapy.
- Early liaison with microbiologists is vital to ensure patients are given appropriate broad spectrum cover.
- Patients with HIV and those post HSCT can have their own unique clinical syndromes.

Suggested reading

- Warrell, D.A., Cox, T.M., Firth, J.D., Benz, E.J. (2003). Oxford Textbook of Medicine. Oxford: Oxford University Press.
- Gea-Banacloche, J.C., Opal, S.M., Jorgensen, J., Carcillo J.A., et al. 2004. Sepsis associated with Immunosuppressive medications: An evidence based review. *Critical Care Medicine* 32;11 S578-S590.
- Huang, L., Quartin, A., Jones, D., Havlir, D.V. (2006). Intensive Care of Patients with HIV Infection. *New England Journal of Medicine*, 355;2 173-181.
- Morris, A., Masur, H., Huang, L. (2006). Current Issues in the Critical Care of the Human Immunodeficiency Virus-Infected Patient. *Critical Care Medicine*, 34;1 42-49.

- Rosen, M.J., Narasimhan, M. (2006). Critical Care of Immunocompromised Patients: Human Immunodeficiency Virus. *Critical Care Medicine*, 34;9 S245-S250.
- Soubani, A.O. (2006). Critical Care Considerations of Haematopoietic Stem Cell Transplantation. *Critical Care Medicine*, 34;9 S251-S267.

Figure 1

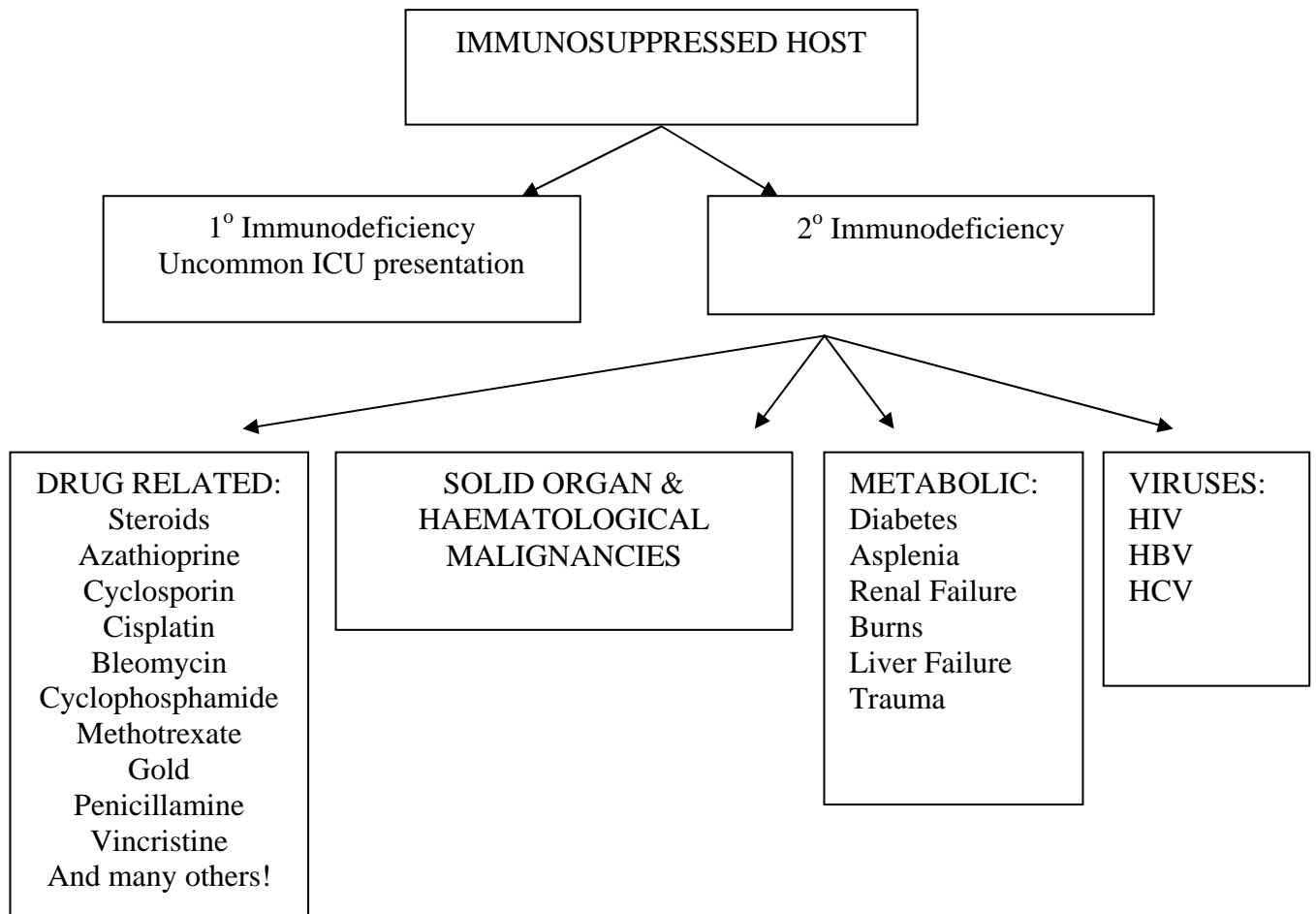


TABLE 1

Nucleoside reverse transcriptase inhibitor	Protease inhibitor:	Non-nucleoside reverse transcriptase inhibitor
Zidovudine	Amprenavir	Efavirenz
Abacavir	Fosamprenavir	Nevirapine
Didanosine	Indinavir	
Emitricitabine	Lopinavir	
Lamivudine	Nelfinavir	
Stavudine	Ritonavir	
Tenofovir	Saquinavir	
Zalcitabin		