Immunocompromised patients

Clinical problems

Update July 2010

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# Immunocompromised patients

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LEARNING OBJECTIVES

After studying this module on Immunocompromised patients, you should be able to:
  1. Recognise the immunocompromised patient in ICU
  2. Manage the immunocompromised patient
  3. Understand the immune response in the critically ill patient
  4. Discuss therapies that result in immune modulation
  5. Prevent infection in the immunocompromised patient

FACULTY DISCLOSURES

The authors of this module have not reported any disclosures.

DURATION

7 hours

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Many patients in the Intensive Care Unit (ICU) are immunocompromised. In some, immunosuppression is easily apparent, especially when caused directly by underlying disease (such as a haematological malignancy) or treatment (such as drugs to prevent organ rejection or as a side effect of cancer chemotherapy). In others, immunosuppression is less apparent and is induced by the underlying disease, for example following traumatic injury or sepsis, or as a response to therapies provided during intensive care such as steroids.

Immunosuppression itself does not cause pathology but does leave the patient prone to infection. There is no good clinical test to measure the degree of immunosuppression; the clinician must simply maintain a high index of suspicion. The consequences of immune suppression in the ICU highlight the importance of infection prevention and control, as well as surveillance measures to ensure that appropriate treatment is implemented safely and quickly. Intensive care clinicians require a thorough understanding of the mechanisms of immune suppression and the management of patients with immune dysfunction.
1. RECOGNISING THE IMMUNOCOMPROMISED PATIENT IN ICU

Clinical skills primarily underlie both the recognition of the patient at-risk of immune compromise and the assessment of whether a related infection has supervened.

Clinical assessment

Specific aspects of the history may alert you to the possibility that your patient is immunocompromised.

The identification of immunosuppression is inextricably linked to the recognition that the patient is infected. Infection is the major cause of morbidity and mortality in patients with immunosuppression. Thorough investigation to identify the source of infection is essential – see later in the prevention and treatment of infection.

The clinical setting is extremely important in recognising immunosuppression. Immune dysfunction induced by therapeutic intervention will be evident from the history but immune impairment due to underlying disease may be more difficult to recognise. Inherited immune deficiencies often have characteristic patterns of disease distribution and may be associated with other clinical abnormalities (such as cardiac anomalies).

A practical approach to identifying the immunocompromised patient is:

- Patient history
  Concurrent disease
  Drug/alcohol history
  Current medication, for example cancer chemotherapy
  Weight loss
  Occupational history: risk of asbestos or other carcinogen exposure
  Social history: HIV (or viral hepatitis) risk – male homosexuality/men who have sex with men (MSMs), workers in the sex industry, intravenous drug users
  Medical history: post splenectomy status, recent hospitalisation or antibiotic therapy; other relatives with symptoms may provide clues as to the source of infection
  Family history: a young patient with recurrent infections may have an inherited immunodeficiency. A history of childhood illnesses may also be relevant
  Travel history may be pertinent
  Patients with haematological malignancies rarely present undiagnosed to the ICU but bruising, bleeding, weight loss, night sweats or lymphadenopathy may suggest the diagnosis.

50% of ICU admissions, in patients with cancer, are related to infection. 80% of patients with cancer-related neutropenia are admitted with documented infections.
• Examination – Does the patient have
  Signs of chronic disease, e.g. finger clubbing, ascites?
  Palpable lymphadenopathy? Is there a palpable spleen?
  Signs of chronic steroid therapy?
  Are there potential ports of entry for infection? e.g. tunnelled catheters, ventriculoperitoneal shunt, urinary catheter
  The critically ill patient is frequently unconscious or unable to give a good history. Look for visual evidence of immunosuppression – e.g. arterio-venous fistula, sternotomy scar for heart transplant, 'Mercedes Benz' scar following liver transplantation, transplanted kidney.
  Nutritional status – does the patient appear to be malnourished?
  Consider the possibility of gastrointestinal disease e.g. inflammatory bowel disease or unusual diseases such as helminth and tropical parasites.

For more information on history-taking and examination, see the PACT module on Basic clinical examination.

In the next five patients admitted to your ICU, identify the factors that might compromise their immune function.

In the International Code of Botanical Nomenclature 2001, Pneumocystis carinii was renamed P. jiroveci and it was recategorised from protozoan to a fungus. PCP is now the approved acronym for pneumocystis pneumonia. Pneumocystis carinii now refers only to a rodent pathogen.

A 54-year-old married man was admitted to our hospital in respiratory distress necessitating immediate intubation upon admission. His wife, who had called the ambulance, gave a history of dry cough and increasing fatigue for four weeks prior to admission. He was taken to the intensive care unit and commenced on benzyl penicillin and ciprofloxacin. Chest radiography revealed a ground glass appearance and hydrocortisone, trimethoprim-sulfamethoxazole and acyclovir were added, pending a definitive diagnosis. There was no other significant history from his wife but on examination, cervical lymphadenopathy was found. Lymphopenia was noted on the full blood count. A few hours after admission, a man claiming to be a partner arrived on the unit and informed us that the patient had had extramarital sexual encounters. The patient underwent bronchoscopy and an HIV test and the diagnosis of PCP secondary to HIV infection was made.

Infection in the immunocompromised patient

The investigation of infection in patients with immune suppression involves the identification of the cause of infection (using imaging, microbiological and serological testing) and the investigation of the degree of immunosuppression.

The search for infections in the immunocompromised patient is often difficult and requires tenacity. A positive diagnosis of the infectious cause improves the chance of recovery.
Although imaging may identify a source of infection, it does not contribute to the identification of the pathogen in most cases. Imaging may simply confirm your suspicions and direct further microbiological sampling. For example, the site of an abscess may be defined so that surgical drainage can be carried out.

A chest **radiograph** may reveal tuberculosis or bronchiectasis both of which are associated with ongoing low level immunosuppression.

**Ultrasound** may also be useful for identifying and draining fluid-filled structures (for instance safe drainage of pleural effusions) and can be carried out in the ICU.

**CT scans** are a useful diagnostic tool but transfer to the radiology department must be undertaken by appropriately trained personnel. Certainly chest CT scans are more sensitive than plain chest films. High resolution CT scans of the chest can help in the diagnosis of suspected invasive fungal infection (IFI). Imaging of other areas (e.g. nasal sinuses) should be considered when searching for potential sources of infection.

**Magnetic Resonance Imaging (MRI)** is usually reserved for patients with neurological disorders. Monitoring and ventilating patients in the MRI scanner requires special MRI-compatible equipment and should be performed in consultation with the MRI department. As machines become more powerful and scan times are reduced, use of MRI in the critically ill may increase.

**Other imaging possibilities.** Occasionally, the **nuclear medicine department** may be helpful in making a diagnosis. **White cell scans** and **gallium scans** are sometimes used to identify abscesses within deep tissue (such as a psoas abscess).

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**Warning:** Transferring the patient to an imaging department presents a challenge to the intensivist. A risk assessment is made prior to transfer to ensure that the patient does not come to any harm whilst away from the ICU.

**Exercise:** Write an assessment of the risks and benefits of transferring the patient from the ICU to the scanner. Will the results of the scan change or enable more focused therapy? Do these benefits outweigh the risks?

You will find additional information about various imaging techniques and patient transfer in the PACT modules on Clinical imaging and Transportation.

**Microbiological investigation/Septic work-up**

*Sending adequate and appropriate samples to the microbiology laboratory is a key aspect of managing the immunocompromised patient; the most important intervention, in the patient with severe sepsis, is the timely (within 1 hour) commencement of appropriate antimicrobial therapy together with concurrent resuscitation.*


PACT module on Sepsis and MODS

Microbiological examination of fluid- or tissue specimens involves both qualitative culture and, in many cases, quantitative analysis. For example, for the diagnosis of ventilator-acquired pneumonia (VAP), combined qualitative and quantitative analysis is often performed on bronchoalveolar lavage (BAL) fluid or tracheal aspirates.


Microbiological analysis can be performed on practically any specimen. Most frequently, sputum, urine and cerebrospinal fluid. Urine, CSF and sputum samples can be immediately examined usually using Gram staining. Additionally, samples may be cultured under various conditions and using a range of growth media.

Serum samples can be analysed for evidence of an acute immune response by measuring non-specific antibodies, e.g. cold agglutinins in *Mycoplasma pneumonieae*. However, it is important that convalescent samples are analysed to confirm that the infection is acute.
Some bacteria produce toxins that can be detected in body fluids e.g. *Clostridium difficile* toxin in the stool of patients with diarrhoea.

Microbiological cultures may take several days (and in the case of mycobacteria, several weeks) to identify an organism. The need for immediate therapy obliges the clinician to use empiric antibiotic therapy for patients with signs of infection – unexplained fever, rigors, hypotension, requirement for circulating volume replacement, tachycardia, tachypnoea or acidosis. This sometimes leads to a stepwise escalation in treatment (if there is not an efficacious response to the first-line antibiotics) during which further antimicrobials are added to broaden the spectrum of cover over several hours or days. For example, initial failure of conventional broad-spectrum antibacterial agents often prompts the addition of an antifungal agent in high-risk groups.

In the hospital setting and in patients already mechanically ventilated, nosocomial infection can be difficult to diagnose with certainty; it is known that under those circumstances inadequate empirical therapy is associated with a worse outcome. In this setting broad antimicrobial cover is often employed, guided by local patterns of bacterial flora and resistance patterns. This broad-spectrum approach is then followed by de-escalation as diagnostic information becomes available.


This empiricism, while necessary and of undoubted benefit, arguably results in over-treatment of some patients. This is especially true of antifungal therapy, where it is estimated that fewer than 15% of neutropenic patients with a fever actually have invasive fungal infection. Until there is an improvement in the rapidity and accuracy of the available diagnostic tests, this approach is unavoidable. However, as soon as culture results are available, anti-infective therapies should be reviewed to allow more focused treatment. This is important to limit the emergence of resistant organisms, as well as to reduce the risk of antibiotic side-effects.

In solid organ transplant recipients, there must also be a high index of suspicion for viral infection. CMV (cytomegalovirus) serostatus mismatch (where the donor is sero-positive for CMV but the recipient is serologically negative) should be treated prophylactically following transplantation. CMV reactivation must be treated aggressively if there is any sign of deterioration. Monitoring of CMV levels by polymerase chain reaction (PCR) is important in patients at risk.
Pneumocystis (P. jiroveci) pneumonia

This infection occurs in patients with cell-mediated immunosuppression and is now seen most commonly in patients with AIDS. It is relatively uncommon in patients following transplantation and cytotoxic agent treatment because of the protocolised use of antibiotic prophylaxis.

Serological investigations

Difficulties in reaching a microbiological diagnosis with conventional cultures have prompted the development of several novel approaches. These include:

- Antigen testing for cryptococcus and galactomannan (a cell wall constituent of Aspergillus species);
- Quantitative PCR for DNA (CMV, EBV, herpes simplex);
- Reverse transcriptase PCR (rtPCR) for RNA (HIV);
- Urinary antigen for Legionella pneumophila;
- PCR for HSV and EBV;
- Mycelial phase antigen for Histoplasma capsulatum.


Investigation of immune deficiency status

Remember, a defect in any of the components of the immune system can result in immune compromise.

Q. Which routine investigations are likely to detect immune compromise?

A. There is no single definitive test of immune function. Qualitative markers of immunosuppression include the presence of neutropenia, lymphopenia or hypogammaglobulinaemia. Plain radiography of the chest may reveal atypical appearances (PCP or tuberculosis) suggesting the possibility of immunosuppression.
**Full blood count**

The white cell population consists of five sub-types: neutrophils, lymphocytes, monocytes, eosinophils and basophils. A differential count may assist in the diagnosis of specific disorders.

Neutrophils have a key role in defence against bacteria, but are also involved in protection against fungi and viruses. The absolute number of circulating segmented neutrophils (absolute neutrophil count; ANC) is a predictor of infection risk. As the ANC falls below $1 \times 10^6/l$, susceptibility to infection increases dramatically. In certain diseases, such as myelodysplastic syndrome, neutrophil function is abnormal even when the neutrophil count is normal.

**Q. How does the differential white cell count change during a bacterial infection? List examples of diseases where there is an isolated rise in one of the leukocyte subsets.**

A. Cytokine expression (especially IL-6) during acute bacterial infection causes demargination of neutrophils and a raised neutrophil count. There is often a 'left shift' in the morphology of the neutrophils on microscopy because of the increase in immature forms. In severe sepsis, consumption of neutrophils and bone marrow suppression may cause a neutropenia and so a neutrophilia or neutropenia should never be ignored.

**The differential white cell count**

Factors that can lead to changes in specific white cell subsets include:

- **Neutrophilia:**
  - Acute infections (by far the commonest cause from bacterial, viral and fungal agents)
  - Administration of corticosteroids and Cushing's disease
  - Metabolic; occurs in diabetic ketoacidosis, pre-eclampsia, status epilepticus, status asthmaticus and uraemia, especially uraemic pericarditis
  - Acute haemorrhage
  - Malignant neoplasms (both solid organ and haematological)
  - Poisoning; with lead, mercury, digitalis, camphor, antipyrine, phenacetin, quinidine, pyrogallol, turpentine, arsphenamine, and venoms
  - Hereditary and idiopathic.

- **Lymphocytes**
  - Pertussis or whooping cough (*Bordetella pertussis*) is frequently accompanied by a lymphocytosis (usually $20.0–30.0 \times 10^9/l$, but may exceed $50.0 \times 10^9/l$) of small mature appearing lymphocytes.

- **Monocytes**
  - Monocytosis (monocytes $>1.0 \times 10^9/l$ in adults) occurs most frequently in the recovery phase of infection, but is also seen in myeloproliferative disorders. Monocytosis may result from viral, fungal, rickettsial, and protozoal infections
  - Phagocytosis of erythrocytes, leukocytes, and platelets by monocytes and histiocytes is seen in the 'haemophagocytic syndrome' which is associated with viral or bacterial infections and T-cell malignant lymphoma.
Task 1. Recognising the immunocompromised patient in ICU p.8

- **Eosinophilia:**
  Allergy, parasitic diseases are the most common but it may also be seen in: liver cirrhosis, Loeffler syndrome, Vasculitis (Churg-Strauss syndrome), tumours (lymphoma), dermatitis herpetiformis, malignant eosinophilic syndrome, hypereosinophilic syndrome.

- **Basophilia**
- **Chronic myeloid leukaemia**
- **Allergic reactions**

A low total lymphocyte count may be seen in patients with AIDS and bone marrow depression but lymphopaenia may also occur in patients receiving steroids azathioprine or mycophenolate, those with adrenal suppression, severe malnutrition, prior antilymphocyte therapy and in Guillain-Barré syndrome (see the PACT module on Neuromuscular conditions). While the total lymphocyte count is important, the T helper cell or **CD4 cell count** (see later) can be used to quantify the risk of infection. The CD4 count is used as a prognostic indicator, along with the viral load, in HIV infection and AIDS.

**Biochemical markers of infection**

C-reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) are non-specific markers of inflammation. The ESR is no longer routinely performed in most ICUs. Some units use the daily change in CRP as an early warning of impending infection although current evidence suggests it has little utility as a predictive marker, tending to rise only during or after the onset of sepsis.


Procalcitonin is used as a bedside test of impending sepsis. Whilst not currently in routine use, there is evidence to suggest it may have a role in the diagnosis of sepsis in the critical care setting, including patients with immunocompromise such as haemato-oncology patients.


TREM (triggering receptor on myeloid cells) -1 is a molecule expressed on phagocytic cells in response to infection with bacteria or fungi and is also elevated during a systemic inflammatory response. TREM-1 has been shown to be a sensitive and specific marker for infection in critically ill patients and may also be useful for prognosis. However, the use of TREM-1 is not routine at present.


**Note**

Immunosuppression is not an all or nothing phenomenon; there are degrees of immune compromise. Similarly immune function is not static and can change during the course of an illness.

Certain specific tests of immune function exist. Most of these tests are research tools and are not performed frequently in the critically ill.

**Other tests of immune function**

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<th>Innate immune response</th>
<th>HLA-DR expression on circulating monocytes</th>
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<td>Mannose-binding lectin levels</td>
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<td>-Polysaccharide antigens</td>
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<td>-Protein antigens</td>
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<td>Tuberculin skin testing</td>
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<td>Blood T-cell numbers and T-cell subsets (CD4 or CD8)</td>
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<td><strong>Absolute neutrophil count</strong></td>
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<td>Tests for oxidative killing mechanisms</td>
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<td>Leukocyte expression of CR3 (CD18 integrins)</td>
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<td></td>
<td>Bacteria or <em>Candida</em> killing assays</td>
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<td><strong>Complement system</strong></td>
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<td>Functional assays of the classical and alternative pathway</td>
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2. UNDERSTANDING THE IMMUNE RESPONSE IN THE CRITICALLY ILL PATIENT

Host defence mechanisms consist of integumental (physical barrier) function, the innate immune response and the adaptive immune response. These are the three components of the host’s defences that invading micro-organisms must breach to cause infection. About 99% of organisms are repelled by the physical barriers. Approximately 1% of organisms are eliminated by the innate response, leaving a tiny proportion (estimated to be 0.1%) to be killed by the adaptive response.

The three layers of the immune response

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<th>Physical barriers</th>
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<tr>
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<td>mannose-binding lectin, phagocytic cells,</td>
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<td></td>
<td>natural killer cells, complement system, acute phase</td>
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<td></td>
<td>proteins</td>
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<tr>
<td>Adaptive immune response</td>
<td>humoral response, cell-mediated response</td>
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Physical barriers

The physical (integumental) barriers consist of the skin and epithelial covering of mucosa. Other physical barriers include stomach acidity and cilia on respiratory epithelium whose natural beating moves foreign material up the airway so that it can be expelled by coughing. The normal epithelial bacterial flora, e.g. in the pharynx, offers an additional layer of defence against invasion by pathogenic organisms by competing with pathogenic strains for nutrition and space and producing antimicrobial substances that inhibit their growth.

Kartagener syndrome is a hereditary disease affecting one of the physical barriers to infection. The syndrome consists of a triad of situs inversus (transposition) of the viscera, abnormal frontal sinuses and immobility of the cilia, causing chronic pulmonary infections such as bronchiectasis and sinusitis.
THINK: about the ways in which the physical barriers of the immune system are breached in patients being treated in the intensive care unit.

The innate immune response


The innate immune system is capable of reacting to foreign antigen in the absence of previous exposure. It is a rapidly acting, non-specific first line of defence against invading organisms and consists of phagocytic cells induced by a variety of cytokines, natural killer cells (a subset of lymphocytes) and protein cascades such as the complement system. Only when the innate immune system is overwhelmed, bypassed or evaded does the adaptive immune system come into play.

The host response is initiated through a wide variety of pattern recognition receptors (PRR) on the surface and within cells of the innate immune system. These include phagocytic cells such as neutrophils, mast cells, dendritic cells and natural killer (NK) cells, a subset of T-lymphocytes. The PRR respond to unique cellular constituents not found in vertebrates. These are referred to as pathogen-associated molecular patterns (PAMPs) and include cell surface proteins, glycoproteins and other cellular constituents such as DNA. Lipopolysaccharide (LPS) and lipotechoic acid are components of the cell walls of Gram-negative and Gram-positive bacteria respectively. Other PAMPs include beta-glycans derived from the cell walls of fungi and bacterial DNA. In addition to PAMPs, PRR are activated by a number of danger-associated molecular patterns (DAMPs). DAMPs are molecules produced by host cellular damage such as high-mobility group box (HMGB), heat shock proteins and S100 proteins that are released following trauma or burn injury. As well as triggering an innate immune response, DAMPs amplify the response to PAMPs.

Binding to PRR activates a cascade of intracellular signals resulting in the activation of cytosolic nuclear factor κB (NF-κB). NF-κB binds to transcription sites within the nucleus inducing an array of ‘inflammatory’ genes. These include genes that encode for acute phase proteins, pro-inflammatory cytokines, coagulation factors and inducible nitric oxide synthase.

Defects in NF-κB activation are associated with an increase in the incidence of immunosuppression and septic shock.

Task 2. Understanding the immune response in the critically ill patient p.12


Acute phase reaction


Following Toll-like receptor engagement and the activation of pro-inflammatory cascades, soluble pattern recognition receptors (PRR) are secreted by the liver, vascular endothelium and innate immune cells. These PRRs are part of the acute phase response that includes a heterogeneous group of approximately 20 proteins, including a number that can be considered functional ancestors of antibodies. They are highly conserved in the animal kingdom. Pentraxin is a term that was first used for the prototypical acute phase protein, CRP (C-reactive protein). This term was coined because of its ultrastructural appearance. CRP and serum amyloid P (SAP) are short pentraxins and are produced in the liver in response to IL-6. PTX3 is a long pentraxin produced widely throughout the body. The pentraxins are multifunctional and interact with a number of ligands including complement, extracellular proteins, apoptotic cells, extracellular matrix and pathogens. They are important in the innate defense against many pathogens including bacteria, viruses and fungi but appear to be relatively specific individually. For example PTX3 shows activity against fungal infection and SAP against viral infection in the respiratory tract. Other acute phase proteins have different functions. Mannose-binding lectin (MBL) binds to repeating sugar moieties, fibrinogen enhances coagulation and ferritin binds iron reducing its availability for microbes.

Mannose-binding lectin is involved in the defense against a wide range of bacterial, viral, fungal and protozoal pathogens. MBL binds to repeating carbohydrate moieties and directly or via complement activation, opsonises a broad range of pathogens for phagocytosis.

MBL gene polymorphisms are common in the general population. There are multiple genetic variations resulting in widely varying serum concentrations. As a consequence MBL is the most commonly deficient molecule in the innate immune system. In the UK population, 2–7% are seriously deficient leading to an increased risk of infection. Children deficient in MBL are particularly at risk of meningococcal disease. In adults MBL deficiency has been associated with an increased risk of severe sepsis, in particular from encapsulated organisms as well as worse outcomes.

Q. In which situations will an inherited reduction in MBL result in a particularly severe deficit in the immune response?

A. In situations where adaptive immune response is already compromised. For example, following bone marrow transplantation or when immunosuppressive drugs are used. Interestingly, patients transplanted with a liver from a donor, later found to be deficient in MBL, have an increased risk of infection and organ failure post transplantation.
Q. What genetic factors contribute to the severity of disease states seen in the ICU?

A. It has been shown that patients with decreased expression of mannose-binding lectin have an increase in severity of meningococcal septicaemia.

THINK: What is the role of genetic polymorphism in the severity of disease states seen within the ICU?

Other plasma proteins decrease – the so-called ‘negative acute phase proteins’. Classically albumin falls acutely, as do transferrin and transcortin. It has been suggested that this reduction in plasma binding sites increases the free concentration of hormones during times of acute stress.

The functions of the acute phase proteins are complex and deficiencies are associated with complex disease states including autoimmune disorders and cardiovascular disease. Variation in the CRP gene promoter is associated with systemic lupus erythematosus (SLE), a condition associated with a number of primary immunodeficiencies.


The adaptive immune system

The adaptive response depends on the clonal selection of lymphocytes predestined to recognise the foreign antigen.

Antigen presentation

Dendritic cells play the major antigen-presenting role, although other cells such as monocytes and macrophages are also able to fulfill this function. Initiation of the adaptive response involves phagocytosis and processing of foreign antigen by antigen-presenting cells. Presentation takes place within lymphoid tissues (lymph nodes and spleen). Fragments of bacteria are opsonised and presented within the clefts of cell surface proteins known as the class II major histocompatibility complex (MHC). These proteins, HLA-DR, -DP, -DQ, interact
with the cell surface receptors of T lymphocytes and are directly responsible for the initiation of the adaptive immune response. The activated T cells, CD4 or 'helper' lymphocytes, secrete cytokines to recruit and complete the immune response. Other families of activated lymphocytes become memory cells ready for subsequent infection.

B lymphocytes express antibody on their surface and are activated by soluble foreign antigen. Whole antigen is internalised, processed and expressed on the surface in association with class II MHC proteins. The clonal selection of plasma cells producing high-affinity antibodies is dependent on the assistance of activated CD4 T lymphocytes (hence 'helper' cells) in association with the B cell MHC-antigen complex and the T-cell receptor within lymph node follicles.

Acquired defects in antigen presentation are seen in critically ill patients. Reduction in HLA-DR expression on circulating monocytes is associated with adverse outcomes in patients following major trauma and critical illness.


**T helper cells**

CD4 or T helper cells can be split into subsets that initiate the differing arms of the adaptive response. Th1 cells are 'pro-inflammatory' and produce gamma interferon and interleukin 2. They are important in stimulating cell-mediated immunity and are responsible for inflammation at the site of infection. Th2 cells are anti-inflammatory and produce interleukin 4, interleukin 5 and interleukin 13. They are essential for B lymphocyte clonal expansion, tissue healing and the production of highly specific antibody. The differentiation of precursor Th0 cells into the two subtypes, is dependent upon local cytokine concentration, antigen load and mode of antigen presentation.

The ratio of Th1 to Th2 cells is important as they produce different patterns of cytokine response. Th1 and Th2 responses appear to be mutually exclusive as each response initiates reciprocal inhibition of the other.
There is renewed interest in the use of stress dose glucocorticoids for the treatment of septic shock. Augmentation of the compensatory anti-inflammatory response syndrome (CARS) may be one mechanism through which they exert beneficial effects.

Compensatory anti-inflammatory response syndrome

The molecular biology of the systemic inflammatory response is complex. Since it was first recognised that inflammation is important in the pathogenesis of sepsis it has become apparent that the induction of the pro-inflammatory cytokine cascade is only half of the story. Just as coagulation is a balance between the pro-coagulant and anticoagulant cascades, so the immune system has developed an anti-inflammatory system to counterbalance the pro-inflammatory process.

This process can be seen in animal models of caecal ligation and puncture. As early as 24 hours following the initial insult, septic animals have a markedly impaired ability to clear a secondary intrapulmonary challenge of bacteria compared to non-septic control animals. This effect persists for many weeks following the initial insult and is apparent in patients within the intensive care unit who are 'anergic' i.e. do not respond to an immune stimulus, and at risk of developing infections with organisms of low virulence that you would normally expect only in seriously immunocompromised patients, e.g following cancer chemotherapy or in those with haematological malignancy.

The initial systemic hyperinflammation is caused by production of inflammatory cytokines, especially tumour necrosis factor-α (TNF-alpha), interleukin 1, interleukin 6 and interferon gamma.

The causes of immunosuppression in critical illness include:

- Change in lymphocyte sub-populations so that Th2 cells predominate
- Anergy – the lack of reaction to an immune stimulus
- Loss of adaptive immune cells via apoptosis
- Direct immunosuppressive effect of apoptotic cells
- Loss of lymphoid tissue
- Reduction in expression of MHC II (HLA-DR) on macrophages
- Effects of drugs (e.g. sedatives, inotropes)
- Production of anti-inflammatory cytokines (e.g. transforming growth factor β1, interleukin 10, interleukin 13)
- Other causes include neuroendocrine, metabolic and hormonal changes

Possible course of pro- and anti-inflammatory interactions

This graph depicts changes in immune function, either pro- or anti-inflammatory, over time following an acute event. The dashed line at the centre represents unity, and the coloured lines represent the response in three hypothetical patients

Anti-inflammatory cytokines and soluble receptors are produced in large amounts during sepsis. They downregulate production of pro-inflammatory cytokines and have been shown to protect animals from sepsis and endotoxin-induced shock. Interleukin 10, interferon α, transforming growth factor β, interleukins 4, 6, and 13 are known to have anti-inflammatory effects. Interleukin 6, for example, induces a broad array of acute phase proteins that help to limit inflammation, such as α-1-acid-glycoprotein or C-reactive protein. However, evidence suggests that the excessive production of anti-inflammatory mediators is associated with a worse outcome. In fact, increased IL-10 levels and IL-10 to TNFα ratio are associated with a poor outcome following sepsis. IL-10 acts as a potent inhibitor of pro-inflammatory cytokine production and also inhibits the expression of MHC class II and NF-κB. Monocyte deactivation occurs in patients with systemic inflammatory response syndrome (SIRS)/sepsis from many causes. The cells lose the ability to mount an inflammatory response and instead switch to the production of anti-inflammatory IL-10 and IL-1ra. Another major characteristic of monocytes in patients with sepsis and severe SIRS is a decrease in the expression of HLA-DR (MHC class II). The reduction in HLA-DR inhibits the monocytes' ability to interact with lymphocytes and induce an adaptive immune response. Clinical recovery is accompanied by normalisation of HLA-DR expression and cytokine-producing capacity, which reflects a functional reconstitution of the innate immune response.

The glucocorticoid receptor (GR) and nuclear factor κB (NF-κB) are transcription factors with opposite effects on immune and inflammatory responses. These receptors can translocate into the nucleus where they regulate gene expression and thus regulate the immune response. Glucocorticoid hormones, via GR, suppress inflammation by inhibiting the transcription of several cytokines, chemokines and cytokine receptors. Activated NF-κB, on the other hand, enhances the expression of many of the cytokines and chemokines that are repressed by GR. In fact the activated GR can be considered an antagonist to NF-κB.
**The systemic inflammatory response and the compensatory anti-inflammatory response**

The full article plus figure is available at http://edrv.endojournals.org/cgi/content/full/20/4/435
3. MANAGING THE IMMUNOCOMPROMISED PATIENT

Clinical management is considered under the headings of ‘neutropenia’ and of the possible site-specific infections.


The neutropenic patient

Neutropenia is most often induced by cancer chemotherapy or conditioning prior to stem cell transplantation (SCT). The frequency and severity of infection is inversely proportional to the neutrophil count. The risks are particularly high when the count drops to below 0.1 x 10^6/l. You can find further information about the side effects of cytotoxic drugs on the following website http://www.bccancer.bc.ca/HPI/DrugDatabase/default.htm

Bone marrow suppression is a consequence of most cytotoxic drugs. It may be regarded as a side effect when treating solid tumours or a treatment effect when they are used in haematological malignancy. Both the degree of myelosuppression and the length of time taken to recover are proportional to the intensity of the treatment. Those subjected to myeloablative regimens used for conditioning the bone marrow for transplantation represent a particularly challenging group when admitted to the intensive care unit.

The rate of decline and the duration of neutropenia are also important prognostic factors and correlate with severity of infection and outcome. Some of the other factors dictating outcome relate to the severity and nature of the underlying illness, nutritional status and the function of physical barriers to infection (integumental function).

Fever in the neutropenic patient

Infectious complications remain the most important cause of death in patients with haematological malignancies. Aggressive investigation and early institution of broad-spectrum antibiotic therapy are mandatory.

See PACT module on Pyrexia

Q. A patient with neutropenia develops fever. How would you approach investigation and treatment?

A. Any neutropenic patient who develops fever should be investigated and, if sepsis is suspected, immediately commenced on targeted or broad-spectrum antibiotics. Investigations should include blood cultures and chest X-ray. Other investigations will

All cytotoxic drugs, with the exception of vincristine and bleomycin, may cause bone marrow suppression. This commonly occurs 7 to 10 days following administration, but is delayed with certain drugs such as carbustine, lomustine and melphalan

Fever in this context is defined as central temperature >38 °C on two occasions separated by more than two hours or a single episode >38.3 °C
depend on the site specificity of the signs and symptoms. The removal of long-term indwelling intravenous catheters should be considered and if being conserved, it as appropriate to try to exclude the catheter as the source of sepsis by quantitative or timed blood cultures taken simultaneously from the CVC and peripheral blood. If the catheter is being conserved, a possibility is to instill appropriate antibiotics into the catheter lumen as ‘antibiotic lock therapy’. Approximately 80% of patients with neutropenia and fever are considered to be infected but the organism is identified in less than 50%. Localising signs and symptoms are often absent but if present help to guide initial antibiotic choice and duration of therapy.

**Initial therapy**

The first epidemiological studies of infection patterns in neutropenic patients were conducted in the 1970s. Since then there have been considerable changes in the nature of causative pathogens. The predominant infecting organisms have changed during this time from more susceptible predominantly Gram-negative bacteria to multiresistant Gram-positive bacteria (S. aureus, enterococci), more resistant Gram-negative bacteria (P. aeruginosa, Acinetobacter, Enterobacter spp.) and fungi. Many factors have influenced this change including increased patient survival, use of broad-spectrum antibiotics selecting for resistant organisms and the increased use of indwelling intravenous catheters and devices.

Fundamental to the successful management of patients with febrile neutropenia is the prescription of effective antibiotics. As mentioned above, current available diagnostic tests are not sufficiently rapid or precise to exclude infection and broad-spectrum antibiotic cover, prescribed at the earliest opportunity, reduces the risks associated with delayed treatment.

The choice of antibiotic regime will depend on local practice and regional infectious epidemiology. The following factors should be considered:

- The apparent site of infection (the working diagnosis)
- The most likely infecting organism(s) – related to the above
- Local resistance patterns
- Pre-existing organ dysfunction
- Patient allergies
- Previous antibiotic exposure.

There are several approaches possible to the prescription of antibiotics at the onset of fever/sepsis in a neutropenic patient. Traditionally a β-lactam combined with an aminoglycoside has been the initial empiric therapy of choice. Concerns regarding aminoglycoside toxicity and the development of extended spectrum cephalosporins, carbapenems and ureidopenicillins, have led to treatment with a single agent in some institutions. Monotherapy with a carbapenem (imipenem-cilastatin, meropenem), an extended spectrum antipseudomonal cephalosporin (such as ceftazidime or cefepime) or piperacillin/tazobactam can be used. Recent evidence suggests that the use of an aminoglycoside in addition to these monotherapeutic agents does not confer a significant advantage.
The use of additional antibiotic therapy to treat resistant Gram-positive bacteria such as vancomycin, teicoplanin or linezolid is controversial. In many countries the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and glycopeptide-resistant enterococci is high. The temptation to start empiric glycopeptides at the onset of fever can be difficult to resist but the risk factors below give guidance.

Finding evidence of benefit to support this approach is, however, difficult. A number of factors suggest that a glycopeptide should be used:

- Known colonisation with MRSA
- Blood cultures positive for Gram-positive organisms
- Catheter- or device-related infection
- Skin, soft tissue and bone infection
- Recent hospitalisation or period of residency in a nursing home
- Recent prophylaxis with ciprofloxacin or trimethoprim/sulfamethoxazole – known to increase the risk of Gram-positive infection
- Substantial mucosal damage with an increased risk of streptococcal infection
- Evidence of systemic inflammatory response syndrome (SIRS) or organ dysfunction. This is because both of these suggest serious infection and an increased risk of progression to organ failure and death.

In these circumstances, initial empiric treatment should be broader but narrowed later once culture information is available.

Fever/sepsis persisting for 48 hours despite broad-spectrum antibacterial agents warrants the introduction of an antifungal agent. Liposomal preparations of amphotericin B have been the mainstay of treatment, but recent guidelines have advocated the use of newer agents such as the echinocandins (e.g. caspofungin) and extended spectrum azoles (voriconazole) because of their lower toxicity. The use of prophylactic antifungal agents may influence the decision to start therapeutic antifungals.

The type and severity of infection predicts outcome in neutropenic patients. Complex infections involving solid organs i.e. lung, liver, spleen, bones, kidneys, meninges, large areas of skin, have a much worse outcome than isolated bacteraemia, bacteruria or infection of the upper respiratory tract. See the PACT module on Severe infection for more information on fungal infection.


Managing respiratory failure in the neutropenic patient

Neutropenic patients are most commonly referred to the ICU with respiratory failure. Respiratory failure is common following cancer chemotherapy and particularly stem cell transplantation. Infectious causes are found in approximately half of all cases.

Two common forms of radiographic presentation are seen: focal changes suggestive of pneumonia and diffuse interstitial or alveolar infiltrates.

Diffuse infiltrates on the chest X-ray associated with hypoxaemia are commonly seen early in the post engraftment stage. These are often due to acute lung injury and frequently resolve with supportive therapy and diuresis. More severe hypoxaemia may require Continuous Positive Airway Pressure (CPAP) and/or Biphasic Positive Airway Pressure (BIPAP). Non-invasive ventilatory support is used in an attempt to reduce the risks of nosocomial infection associated with intubation of the trachea.

It has become standard practice to manage patients with non-invasive ventilatory support during the last ten years. However recent data has challenged this view (Depuydt et al) although formal randomised trials are required. Guidelines are available for the investigation and management of pulmonary infiltrates in patients with febrile neutropenia.

See also the PACT modules on Respiratory failure and Mechanical ventilation


Q: What further investigations for the aetiology should be considered in a ventilated neutropenic patient with deteriorating lung function?

A: Fungal pneumonia, PCP, viral pneumonia and non-infectious causes should be considered. Investigations may include bronchoalveolar lavage (BAL), high-resolution chest CT and serology for atypical pneumonia. Thorascopic or open lung biopsy is occasionally indicated but carries significant risks and yields are low. Other non-
infectious causes include pulmonary haemorrhage, ARDS and bronchiolitis obliterans organising pneumonia (BOOP).

Fungal infections can be extremely difficult to treat successfully. High resolution CT scanning and BAL will guide therapy and provides an indication of the response to therapy. A diagnostic test based on the detection of galactomannan in blood has a sensitivity of approximately 70% and a good specificity. However, the test often becomes positive after other confirmatory tests and there remains significant debate over the utility of this investigation in clinical practice. Fungal infection usually presents with focal radiographic features and *Aspergillus* is a common aetiology in the immunocompromised patient. It is important that institutions managing patients who may develop invasive fungal infections have protocols for the investigation and management of this complication.

*Aspergillus infection*

*High resolution CT scanning is now the investigation of choice for imaging of respiratory aspergillosis. Common findings include nodules with surrounding ground glass shadowing (see figure) and the ‘halo’ sign. Whilst not diagnostic, such findings are highly suggestive of invasive fungal infection. Wherever possible, confirmation of diagnosis (e.g. by bronchoalveolar lavage) should be attempted.*

The aetiology of pneumonia presenting late following SCT (>100 days) is similar to that presenting early. Diffuse infiltrates may be due to bacterial, fungal or viral infection but chest X-ray infiltrates due to non-infectious causes are more common. These include graft versus host disease and bronchiolitis obliterans. These diagnoses are often made by exclusion of infectious causes, but characteristic changes such as air-trapping which can be seen on high resolution CT of the chest, requires scanning during inspiratory and expiratory phases.

*Managing site specific infection in the neutropenic patient*

Mouth and oesophagus are common sites of inflammation and secondary infection. Mucositis induced by cancer chemotherapy can be severe and presents a portal of entry for infection. Fungal and viral infection must be considered in febrile patients with necrotising ulceration of the mouth. Vesicular lesions imply the presence of herpes simplex.
Sinus tenderness, periorbital oedema or purulent naso-pharyngeal secretions suggest **sinus infection**. CT scanning and referral to the Ear, Nose and Throat (ENT) specialists to facilitate sample collection may be indicated. Fungi (*Aspergillus, Mucor*) should always be considered in a neutropenic patient presenting with sinus symptoms or sinus fluid collections. In the intubated patient, consider replacing a nasogastric tube with an orogastric tube. Nasotracheal intubation is avoided in the ICU.

Intra-abdominal infections are difficult to diagnose in sedated, critically ill patients. However the diagnosis should be considered if the patient fails to improve, in the presence of an unexplained pyrexia and new organ dysfunction/biochemical derangement. A combination of clinical examination, interpretation of liver function test abnormalities, imaging and communication with the surgical team will assist patient management. High serum transaminases may be associated with viral hepatitis or hepatic veno-occlusive disease in patients following SCT. After targeted cultures, polymicrobial ‘abdominal’ antibiotic therapy including cover for anaerobes should be considered. Infection with *Clostridium difficile* should be excluded in all patients with diarrhoea and stool should be sent for toxin analysis. Sigmoidoscopy and biopsy can help with the diagnosis of both *C. difficile* and CMV enterocolitis but should only be undertaken with caution as the alternative, less invasive, CT scanning of the abdomen may be diagnostic. Typhilitis may cause localised abdominal pain and progress to perforation. Treatment includes broad-spectrum antimicrobials against enteric organisms and general supportive measures.

**Outcome of intensive care in patients with neutropenia**


Patients requiring intensive care following SCT have a worse prognosis if they receive donor marrow (allogeneic transplantation) than if they are given their own marrow (autologous transplantation). The need for organ support, in particular intubation and mechanical ventilation, is a poor prognostic sign. The mortality in this group has been reported between 70% and 100% but seems to be improving. There is some recent evidence that the use of non-invasive ventilation may be associated with a reduced mortality in patients requiring ventilatory support.

Huynh TN, Weigt SS, Belperio JA, Territo M, Keane MP. Outcome and prognostic indicators of patients with hematopoietic stem cell transplants admitted to the intensive care unit J Transplant. 2009; 2009: 917294 Epub 2009 Sep 15 PMID 20130763

http://www.cancer.org/docroot/ETO/content/ETO_1_2X_Infections_in_People_with_Cancer.asp
HIV Disease and the lymphopenic patient


HIV is now a treatable condition. The majority of those living with the virus remain fit and well on treatment for many years. While the availability of Highly Active Antiretroviral Therapy (HAART) has transformed the outcome for individuals with HIV infection, a significant number of patients continue to be admitted to ICU with complications, a proportion of whom will die. Infection with HIV is associated with increased susceptibility to infection with more than 100 different viruses, bacteria, protozoa and fungi.

As long-term survival for those with HIV infection has improved, so the indications for ICU admission have changed. In one study, sepsis resulting from bacterial infection was now a more frequent cause of admission than *Pneumocystis carinii* (now called *jiroveci*) pneumonia. Another study suggested that ICU mortality of patients with HIV is comparable to other medical patients. In that study, more than a quarter of patients had newly diagnosed HIV infection. Patients receiving HAART did not have a better outcome.


Late diagnosis has been associated with increased mortality and morbidity and an impaired response to HAART. Only 50 to 70% of HIV positive patients achieve significant virological suppression with HAART and there is a decline in the response to therapy over time. HAART is associated with a number of serious and troublesome side effects which may prevent the patient from taking their full dose, thereby reducing effectiveness. While antiretroviral treatment undoubtedly improves outcomes in the long-term HIV infected patient, the decision to start HAART in the ICU following a new diagnosis of HIV remains controversial. In contrast to the evidence cited above, other studies have suggested that continuing or initiating HAART in critically ill patients improves outcome.
Q. When faced with an acute admission of an AIDS patient in respiratory failure, what therapies would you begin?

A. A third generation cephalosporin such as cefotaxime, along with cover for atypical pneumonias (e.g. clarithromycin) would be appropriate. If PCP is a possibility, treatment with trimethoprim-sulfamethoxazole is indicated, together with hydrocortisone in those who are hypoxaemic. Acyclovir should be given when viral pneumonia is suspected.

Antiretroviral Therapy is associated with many adverse effects and dosing in the ICU can be particularly difficult, particularly in the presence of renal or hepatic impairment. HAART is frequently delivered as combination therapy. For some agents parenteral preparations are not available. All Nucleoside Reverse Transcriptase Inhibitors and protease inhibitors require caution in patients with hepatic impairment. See the AIDSInfo website http://www.aidsinfo.nih.gov/ for more information.

Q. What are the side effects of HAART?

A. An incomplete list is:
- Insulin resistance or diabetes mellitus
- Hyperlipidemia
- Ischaemic heart disease
- Gastrointestinal side effects
- CNS disorders
- Peripheral polyneuropathy
- Renal impairment
- Hepatotoxicity
- Haematological abnormalities
- Allergies
- Lactic acidosis
- Pancreatitis
- Avascular necrosis
- Osteopenia/osteoporosis/osteonecrosis
- Increased bleeding episodes in haemophiliacs


CD4 count is a marker of likely disease progression. CD4 counts can be used to estimate the risks for particular conditions, as shown in the table below.

**CD4 count – a marker of likely disease progression**

<table>
<thead>
<tr>
<th>CD4 count (x 10⁶/l)</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>250-500</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td>150-200</td>
<td>Kaposi’s sarcoma – caused by human herpes virus 8</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>75-125</td>
<td>PCP</td>
</tr>
<tr>
<td></td>
<td>Cerebral toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal meningitis</td>
</tr>
<tr>
<td></td>
<td><em>M. avium intracellulare</em> infection</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Cytomegalovirus infection</td>
</tr>
</tbody>
</table>

Protease inhibitors are associated with lipodystrophy and metabolic effects. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis.

Primary and secondary prophylaxis against infections and the use of HAART has changed the nature, incidence, and presentation of infections due to *Pneumocystis pneumonia* (PCP), *Mycobacterium avium intracellulare* (MAI) and cytomegalovirus (CMV) retinitis. Multidrug-resistant (MDR) tuberculosis (resistant to isoniazid and rifampicin) is becoming an increasing problem among HIV positive individuals in North America and some parts of Europe. Antituberculous treatment requires careful monitoring for drug interactions and toxicity, especially if the patient is receiving HAART. Interactions such as those between the rifamycins and protease inhibitors or non-nucleoside reverse transcriptase inhibitors can lead to lower efficacy or increased toxicity of the anti-retroviral regimen.

Infection following solid organ transplantation

For more information on organ transplantation, see the PACT module on Organ donation and transplantation.

Time line for infection in solid organ transplantation

The spectrum of infection seen following solid organ transplantation (SOT) reflects the organ system involved, the pathogens contaminating the patient’s local environment (whether in hospital, on the ward or at home) or reactivation of quiescent colonisation. For example a respiratory viral infection developing after SOT may be due to reactivation following pre-operative exposure rather than hospital acquired de novo; certain systemic mycoses may also represent reactivation following previous community exposure.

The type of infection will be influenced by time from surgery, the environment, and the degree of immunosuppression.

Infection during the first two months following transplantation

Most infections occurring during the first month post transplantation are related to surgical and technical complications. These include bacterial and Candida wound infections, pneumonias, urinary tract infections, catheter-related sepsis and infected drainage tubes.

Mucocutaneous and rarely visceral herpes simplex virus (HSV) infection is usually due to reactivation of the host's latent strain after iatrogenic immunosuppression. Prophylactic acyclovir has reduced the incidence of HSV infection.

Rarely infection may arise from the donor organ. Bacterial or fungal infections usually cause local complications such as suture line rupture or local abscess. Following cardiac transplantation systemic toxoplasmosis and active herpes simplex virus have been transmitted by the donor organ.

Untreated infection in the recipient prior to operation will become more severe following transplantation and immune suppression.

NOTE: Treat infection before transplantation. Ideally, recipients should be free from infection at the time of transplantation. Antibiotics should be administered if there is evidence of infection in the donor or the recipient. Transplantation is often postponed if there is clear sepsis in the recipient.

THINK: Are there any particular micro-organisms prevalent in your ICU that pose a particular risk to immunocompromised patients? Are these especially common in your country?
Infection during the second to sixth months

The subsequent months are associated with opportunistic infections as a consequence of immunosuppressive therapy. These are due to pathogens such as CMV, *Pneumocystis jiroveci*, *Aspergillus* spp. and other mycelial fungi such as *Nocardia* as well as *M. tuberculosis*. Other viral infections occurring between one and sixth months are Epstein-Barr virus (EBV), hepatitis B & C, human herpes virus 6 and 7. These tend to reactivate and exert clinically significant effects.

Although CMV can occur at the end of the first week following transplantation, it is more common after approximately one month (and for up to six months in lung recipients). CMV may present as invasive disease (such as hepatitis or pneumonitis) or systemic infection (characterised by viral shedding).

10 to 50% of recipients develop CMV disease depending on the serological status of the donor and recipient. It is important to note, however, that CMV infection:

- Occurs most commonly following transplantation with a sero-positive donor
- Causes a variety of clinical presentations
- Can induce graft dysfunction
- Exacerbates immunosuppression.

**Q. How can you recognise CMV infection in the ICU?**

**A.** In immunocompromised patients CMV induces a variety of syndromes including: fever and leukopenia, hepatitis, pneumonitis, oesophagitis, gastritis, colitis, retinitis.

Symptoms often begin with prolonged fever, malaise, anorexia, fatigue, night sweats, myalgia and arthralgia. Investigations may reveal liver function abnormalities, leukopenia, thrombocytopenia and atypical lymphocytosis during these episodes. There may be a dry cough, dyspnoea and hypoxia in those with pneumonia. Chest X-ray findings may include bilateral interstitial or reticulonodular infiltrates beginning in the
periphery of the lower lobes and spreading centrally and superiorly. Localised segmental, nodular or alveolar patterns are less commonly seen. GI involvement may be localised or extensive. Fatal CMV infections are often associated with persistent viraemia and multiple organ involvement. Progressive pulmonary infiltrates, pancytopenia, hyperamylasaemia and hypotension are characteristic. Superinfection with bacterial, protozoa and fungi are common.

Other early manifestations (1-6 months post transplant) of CMV infection include encephalitis, transverse myelitis and cutaneous vasculitis.

**Infection from six months and beyond**

From six months onward the majority of transplant recipients are free from infection. They remain stable with relatively mild immunosuppression. However, those with multiple episodes of acute rejection or those with late chronic rejection who require higher levels of immunosuppression continue to be at high risk of infection. Long-term immunosuppression is also associated with an increased risk of cancers, such as lymphomas related to chronic viral infection with EBV.

Those receiving a liver transplant for complications of hepatitis B infection are at risk of re-infecting their graft. This risk is exacerbated by their immunosuppression. In hepatitis B infection a combination of pooled human hepatitis B immunoglobulin and the antiviral agent lamivudine, is used to prevent re-infection. Lifelong monitoring and therapy are required.

**Timing of other infections following organ transplantation**

Patients with organ transplants are also at risk of developing parasitic infections. These can be due to reactivation of dormant infection, by *de novo* infection following transplantation, or be caused by infection of the transplanted organ.

A wide variety of parasitic infections have been described in patients following a solid organ transplant. In the immunocompetent patient, morbidity and associated mortality are relatively low when one considers the infection burden in some parts of the world (e.g. malaria). In the immunocompromised both morbidity and mortality are considerably increased. The full impact of parasitic infection is difficult to define because of the scarcity of reports. The most common form of acquired infection is with parasites that spend either some or most of their life cycle in the circulatory system or by organisms residing within the transplanted organ.

*Viral infections, post transplant, are dominated by CMV*
Immunosuppression during pregnancy

Pregnancy is an immunosuppressed state. The fetus expresses antigens foreign to the mother as it is genetically different from its host. The maternal immune system tolerates this in most cases and the fetus is not attacked. Direct contact between maternal and fetally-derived trophoblastic cells occurs in the placenta but maternal immune-tolerance explains why pregnant women are at greater risk from certain infections.

Primary infection with herpes simplex virus during the third trimester of pregnancy can be severe and can precipitate critical illness in both mother and fetus. Presentation can be fulminant leading rapidly to multiple organ failure and death. The situation is often compounded by diagnostic delay. Maternal acute liver failure is frequent.

THINK: What is the mechanism of pregnancy-induced immunosuppression?

Immunosuppression following splenectomy

The immune deficit following splenectomy is incompletely understood but such patients will have a life-long increased susceptibility to certain infections particularly those caused by encapsulated bacteria (Neisseria meningitidis, Streptococcus pneumoniae and Hemophilus influenzae). The sites of infection are usually lung, CNS and bloodstream.

Patients who undergo elective splenectomy should be immunised against these organisms prior to operation. Management varies in patients who require splenectomy as an emergency and in whom pre-operative vaccination is impossible. Some specialists believe that immunisation is beneficial in all cases, whilst others recommend life-long prophylaxis with penicillin.

Functional hyposplenism is more common than previously thought. Evidence of reduced splenic function shown by the presence of Howell-Jolly bodies on a peripheral blood film has been reported to be present in 1 in every 200 samples processed in one laboratory. The most common causes are liver disease and celiac disease but many other diseases affect splenic function.

You can find out about the causes of hyposplenism on the following website and the reference below.

http://www.fpnotebook.com/GI/Spleen/Asplnc.htm

4. UNDERSTANDING IMMUNE MODULATION

Recent advances in our understanding of the immune response and especially the mechanisms that curtail the pro-inflammatory cascade prompted re-evaluation of the extent of immnosuppression in the critically ill. There is growing awareness that immune dysregulation makes a significant contribution to immune suppression in the critically ill. Furthermore many of the standard ICU interventions, such as sedation and inotropic support (see below), have immune-modulating effects. This Task will focus on the changes in immune function caused by treatment.

Physical therapies

**Total body irradiation**

Total body irradiation (TBI) is used as a conditioning process before bone marrow transplantation. It is often used in conjunction with cytotoxic drug regimens. Patients develop a profound pancytopenia. These patients rarely enter the ICU during this phase of treatment but of course are prone to a wide variety of infections.

**Plasmapheresis**

Possible indications for plasmapheresis in the intensive care setting include the Guillain-Barré syndrome, myasthenia gravis and thrombotic thrombocytopenia purpura. For more information see the PACT modules on Neuromuscular conditions and Bleeding and thrombosis.

The main immune effects are due to temporary removal of circulating immunoglobulin. Nevertheless, large trials comparing the use of plasmapheresis with intravenous immunoglobulin in the management of Guillain-Barré syndrome have shown no difference in the incidence of infection.

**Blood transfusion**

Immunosuppression following transfusion has been shown to increase the risk of postoperative infection and influences tumour recurrence. These effects are thought to be due to associated white blood cell contamination within red blood cell concentrates. Transfusion of leuko-depleted red blood cells reduces the incidence of fever and antibiotic use but not the incidence of infection.

There may also be immune stimulation either through ABO incompatibility or red cell alloimmunisation leading to red cell antibody formation. This is found especially in patients requiring multiple transfusions.


**Drug therapies**

**Cancer chemotherapy**

Cytotoxic drug regimens cause cytopenia as a result of marrow toxicity. Neutropenia is the main predictor of infection although both T and B lymphocyte function may also be affected. Other side effects of cytotoxic agents include oral mucositis, hyperuricaemia, neurotoxicity and nephrotoxicity. Mucositis is a disabling and common complication of cancer chemotherapy. Good mouth care may reduce its severity. Treatment is difficult and can pose a serious problem in the ICU. Inflamed mucosa may also act as a portal for infection.

**Glucocorticoids** (GCs) are the oldest immune modifying drugs. They have complex immune effects that are dose related. They are widely used in many conditions in which immune activation plays a role in disease activity. Glucocorticoids change lymphocyte populations and increase apoptosis in thymocytes and eosinophils. Polymorphic neutrophils, however, have prolonged life-cycles when steroids are used and there is little difference in macrophage survival.

The use of GCs in critical care has evolved over the last 30 years. Following the recognition that inflammation played an important role in the pathogenesis of critical illness, steroids were used, often in large doses, in an attempt to control the inflammatory processes, but at the expense of an increase in infection and mortality. Despite this, interest remained and further work in ARDS and in patients with shock rekindled interest in the use of GC therapy.

See the PACT module on Sepsis and MODS

GCs have been investigated extensively in patients with ARDS to see if long-term therapy reduces morbidity and mortality. There is some evidence that GCs appear to improve lung function and reduce ventilator days compared to standard therapy, without an increase in infectious complications. However there is an increased risk of myopathy and neuropathy and an increased mortality if GCs are started at least 14 days after the onset of ARDS.

See the PACT module on Respiratory failure

The use of GCs in septic shock has received considerable attention recently. The rationale had been based on supplementing relative adrenal insufficiency rather than inhibition of the inflammatory response. It appears that GC use in septic shock reduces the time on vasopressors regardless of initial response to ACTH.
(i.e. whether the patient has a suppressed adrenal response or not). However, an improvement in mortality has not been proven and subsequent analysis suggests that the biggest trial to date (CORTICUS) was underpowered.

Current recommendations (see reference to Surviving Sepsis Guidelines, below) for the use of GCs in septic shock are that they can be used in patients with vasopressor resistant shock for shock reversal, at the discretion of the treating physician and should be tapered once vasopressors have been discontinued.


http://www.survivingsepsis.org/

**Purine analogues** and antimetabolites were derived as anti-cancer drugs. Azathioprine and 6-mercaptopurine are the only members of this group at present. These agents are metabolised to substances that interfere with DNA and RNA synthesis during clonal expansion, reducing the production of immune cells. The main side effect is bone marrow suppression that limits the dose of azathioprine tolerated.

**Suppression of the immune response to foreign antigens on a transplanted organ**

There were 3513 solid organ transplants in 2008–2009 in the UK and as at July 2010 there were 107 815 patients on the US waiting list for a solid organ transplant

http://www.uktransplant.org.uk/
http://www.unos.org/data

Immunosuppressive agents exert their effects by one or more of the mechanisms below:

- **Altered lymphocyte function.** This is the mainstay of immunosuppressive regimens used today.
- **Sequestration or altered lymphocyte traffic.** New agents are being developed that affect lymphocyte cell traffic.
- **Depletion of lymphocytes.** This results in intense immunosuppression and is now rarely performed.
- **Structural damage to lymphoid tissue.** It is known that lymph nodes play an important role in the immune response. Antigen presentation takes place within lymphoid tissue.
**Immunosuppression for transplantation**

Most immunosuppressive protocols use combinations of agents, in an attempt to reduce dose and toxicity of individual treatments. Standard regimens use a glucocorticoid, a calcineurin inhibitor (see below) and an antiproliferative agent. The newer more selective agents being developed will hopefully result in improved immunosuppression, graft tolerance and a reduction in both immune and non-immune toxicity.

**Immunophilin-binding drugs** (calcineurin inhibitors). The drug category name of cyclosporin A (CyA), tacrolimus (TAC), rapamycin/sirolimus (RM) derives from their ability to bind to immunophilins: cyclophilins (Cps) and FK binding protein (FKBP). They are all derived from immunosuppressive toxins made by bacteria, presumably for the purpose of manipulating the immune response of their hosts they infect. Immunophilins are intracellular protein phosphatases and are abundant and ubiquitous. They play essential roles in cell proliferation, differentiation, and death. CyA engages Cps, and both TAC and RM engage with FKBP forming complexes. The new surfaces of these complexes target important intracellular enzymes and in T cells, prevent cytokine production or cell proliferation. CyA and TAC inhibit the production of IL-2 but sirolimus blocks the response to IL-2 activation, thus preventing the stimulation of T and B cells.

**Mycophenolate** inhibits DNA and RNA synthesis. It is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase. The production of purine nucleotides is reduced causing a relative deficiency in guanine and excess adenine. This effect is limited to lymphocytes because other non-immune cells recycle purines.

*Mode of action of some immunosuppressive agents on T helper cells*
*Adapted from Goddard S, Adams DH. New approaches to immunosuppression in liver transplantation. J Gastroenterol Hepatol 2002; 17(2): 116-126. PMID 11966939*

Legend: -ve means inhibitory. These are Th1 helper cells.
**Protein-based drugs.** Lymphocyte immune globulins (ALG, ATG) are active against surface protein structures. They are derived from animal sera. They have three effects: lysis of lymphocytes, altered traffic and altered function. These drugs are often used at the initiation of immunosuppression or as rescue treatment for acute rejection. They have the potential to induce profound T cell depletion and therefore the risks of subsequent infection are high.

**Interleukin 2 receptor blockade** by humanised murine monoclonal antibodies is a relatively new means of achieving immunosuppression. Daclizumab and basiliximab both block the actions of interleukin 2 but have slightly different pharmacokinetics. Interleukin 2 receptor blockade has been shown to reduce the need for other immunosuppressants and has enabled the use of steroid-free protocols in certain solid organ transplants.

**Modern immunosuppressive regimens** are very successful in the prevention of acute rejection and the preservation of early graft function in solid organ transplantation. Most of these regimens are based around one of the calcineurin inhibitors, cyclosporin or tacrolimus. Now that solid organ transplantation has become routine and rejection less of a problem, it has become apparent that longer term graft and patient outcomes are often dependent on renal function and other side effects of long-term immunosuppression such as increased cardiovascular risk, diabetes and malignancy.

It is well known that renal function is adversely affected by the use of calcineurin inhibitors. Many studies have been performed in an attempt to reduce or eliminate the toxicity of these agents. There has been some success, but often at the expense of an increased risk of infection or malignancy.

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**The use of biologic agents in autoimmune disease and haematology**

Biologic agents are monoclonal antibodies that interact with a number of cell surface receptors and other biologically active molecules.

The field of biologic therapy has expanded rapidly and the rate of development does not appear to be slowing. The numbers of new drugs available and the number of indications continue to grow. There are currently five TNF inhibitors in therapeutic use. They are most commonly used for rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis and inflammatory bowel disease, amongst others.
IL-1 and IL-6 are both pro-inflammatory cytokines important in the pathogenesis of rheumatoid arthritis and have been targeted by biological therapy. The anti CD20 monoclonal antibody rituximab is directed against B-lymphocytes and was first licensed as a treatment for B-cell non-Hodgkin’s lymphoma. It has been used in a number of other disease states including rheumatoid arthritis and SLE.

The immune suppressant effects of biologic agents varies according to the agent and whether it is used in combination with other immune-modulating drugs but most have shown a small but consistent increase in infectious complications associated with their use.

Anti-TNF drugs have been the most studied. Pharmacovigilance studies have shown an increase in opportunistic infections with their use. Some data also suggest an increase in the incidence of hematological malignancy. There is also evidence that the anti-TNF drugs interfere with the important role TNF plays in tuberculosis immunity resulting in a greater proportion of patients presenting with extra pulmonary manifestations.

IL-6 inhibitors such as tocilizumab bind to both soluble and membrane bound IL-6. This agent is used in rheumatoid arthritis and improves functional status and radiographic changes. An increase in infectious complications has been demonstrated.

Combinations of biological agents appear to exacerbate the risk of infection.

**The coincident immunomodulatory effects of commonly used drugs**

The realisation that some of the drugs used routinely in the ICU may be causing harm was highlighted by the observation of an increase in mortality associated with the use of the sedative agent etomidate (first reference, below). This intravenous anaesthetic agent was shown to inhibit basal cortisol production and abolish the stress response. Mortality figures returned to normal following its discontinuation.

In the second reference, the authors found a single dose of etomidate to be a risk factor for relative adrenal insufficiency.

**References**

Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. Anaesthesia 1984; 39(10): 973-981. PMID 6496912


Many drugs have been shown to have more subtle effects on immune function. Agents used for prolonged periods such as sedatives, analgesics and inotropic agents have been studied most extensively.
**Sedative agents**

Propofol, midazolam and ketamine all possess immunomodulatory properties. Phagocytic and chemotactic responses are inhibited in vitro by these drugs as is cytokine release. The latter is variable and depends on the drug and the cytokine studied. However, little work has been performed in vivo and, other than etomidate, it has not been shown that specific sedatives influence mortality.

**Opioids**

Opioids have been implicated in changes in lymphocyte sub-populations with a decrease in natural killer cells and an increase in the percentage of B and T cells. Two hormone axes are affected by opioid administration; prolactin secretion increases whereas cortisol secretion decreases. These changes influence both cytokine synthesis and lymphocyte migration. However, these theoretical effects have not been shown to affect mortality.


**Inotropic drugs**

Lymphoid tissue is closely linked to the autonomic nervous system and is affected both directly, by non-synaptic interaction and indirectly by circulating catecholamines. Antigen presentation and cytokine production are influenced by catecholamines, as are the innate and adaptive immune responses. Immune cells are directly affected via cell surface receptors and by the influence of catecholamines on cytokine secretion.

The nervous system also has an immunosensing function, both directly via the action of cytokines on the brain and via the vagus nerve. There are also a number of humoral mechanisms; cytokines are known to be actively transported across the blood–brain barrier and can enter via the circumventricular regions. In addition sensory vagal afferent fibres detect cytokines peripherally at low concentration. A reflex arc via the efferent vagus has been termed the ‘cholinergic anti-inflammatory pathway’. The vagus secretes acetylcholine that acts on Ach receptors on macrophages and other cytokine producing cells.

Animal models using lethal doses of endotoxin and haemorrhagic shock have shown that electrical stimulation of the efferent vagus considerably attenuates the inflammatory response. In contrast vagotomy increased the concentration of inflammatory cytokines and the severity of shock. During sepsis vagal stimulation results in reduced serum levels of HMGB-1 protein, as has been shown with the acute administration of nicotine in aseptic SIRS.
Epinephrine and norepinephrine both tend to suppress Th1 activities and boost Th2 and humoral responses during antigen presentation. Suppression is also mediated via direct interaction with lymphocytes. Stimulation of the β-adrenoreceptor is associated with effects that are predominantly immunostimulating (induction of TNF-α and interleukin 1β) but also has immunosuppressive consequences (inhibition of TNF-α and interleukin 1β plus induction of interleukin 10). β2 stimulation produces a Th2 response and a predominance of immunosuppressive cytokines. The response of the humoral immune system is more complex. In general there is an increase in antibody production, especially IgE. Immune cells predominately express the β2 adrenoreceptor.


Dopaminergic immunomodulation is dominated by immunosuppressive effects, such as the induction of interleukin 6, the inhibition of TNF-α, the attenuation of the chemoattractant effect of interleukin 8 and the inhibition of endothelial adhesion. Catecholamines also alter the number and function of neutrophils and lymphocytes.

Prolonged catecholamine stimulation in patients with critical illness is an abnormal situation from an evolutionary standpoint and whereas initial catecholamine secretion during stress may induce antibody production, long-term exposure will tend to have an immunosuppressive effect. This probably contributes to the immune dysregulation seen in the critically ill.

THINK about the causes of immunosuppression associated with multiple organ failure.

Modifying the immune system in the critically ill

Clinical trials aimed at reducing the effect of inflammatory mediators by using antibodies against endotoxin, TNF-α antagonists of interleukin 1 or platelet activating factor have proved to be uniformly disappointing. Not only have these agents been found to be of no benefit, but in some cases they may increase mortality.


As well as attempts to dampen the initial pro-inflammatory state associated with early critical illness, efforts have been made to stimulate the immune system in patients showing signs of immunosuppression. One group has tried to
stimulate the immune response with gamma interferon (γIFN). They found an increased expression of HLA-DR on circulating monocytes and an improved outcome in this small but interesting study.


Other drugs have been identified that stimulate immune function and, in the future, may prove to be useful in the critically ill. Imiquimod induces cytokine production from Th1 cells and at present is only licensed for use topically against genital warts. It is hoped that other drugs from the same family may offer more promise in critical illness.

Amifostine is an agent that has been shown to reduce some of the toxic effects of both radiotherapy and some cancer chemotherapy. It is proposed that amifostine is transformed into its active form, the free thiol (WR-1065), more easily by normal cells than by tumour cells, thus offering some buffering from the oxidative stress induced by the chemotherapeutic insult.

Trials using filgrastim (a granulocyte colony-stimulating factor (G-CSF)) were unsuccessful at reducing mortality or the complication rate from pneumonia in adults although early work in neonatal ICUs has produced some promising results. Research in this area is on-going and opinion is contradictory.

In the reference, below, it was shown that GM-CSF could reverse innate immune suppression in sepsis and was also associated with faster clearance of bacteraemia and a trend towards improved survival, although the study was not powered for outcome.


Q. What are the potential complications of stimulating the immune system in severe sepsis?

A. Upregulation of the immune response in severe sepsis might be expected to increase systemic inflammation and worsen organ dysfunction, perhaps counteracting the beneficial effects of enhanced clearance of infection.

Select five patients in the ICU who are receiving drugs with immunomodulatory effects. What are the indications? Find out the effects on the immune status. How do you confirm these?
5. PREVENTING INFECTION IN THE IMMUNOCOMPROMISED PATIENT


PACT module on Infection control strategies

The incidence of nosocomial infections in ICU is between 15% and 40% and is a consequence of concentrating severely ill patients in one site, breaching the integrity of gut and skin and alterations in the patient’s normal flora.


Q. Why does ICU admission alter commensal skin flora?

A. Antibiotic therapy, changes in environmental flora, skin sterilisation during operative procedures and washing with soaps to reduce MRSA colonisation all alter the patient’s natural skin flora.

Hand hygiene

The most important intervention is hand hygiene. Washing hands or using alcohol gel between patient contact dramatically reduces transmission of bacteria.


NOTE Because of the devastating consequences of infection in the immunocompromised patient, prevention is a key responsibility of the intensive care team.
Isolation

Isolation of potentially contagious patients within the ICU should be attempted if practical to reduce the chances of cross infection. Although isolation is recommended for control of airborne spread of pathogens, cross-colonisation with organisms predominantly spread by contact (such as MRSA), may only be reduced by changing behaviour of staff. In the absence of adequate isolation rooms, barrier precautions with gloves and gown combined with good hand hygiene is paramount.

Standards for ICU design

The ICU is a reservoir of resistant infectious organisms. Curtains, walls, floors and air-conditioning are all potential sources of infection. The role of cleaning and decontamination should not be underestimated. At times of local epidemics or outbreaks, the closure of part of or the whole unit should be considered to allow thorough cleaning. Hydrogen peroxide vapour decontamination has been shown to be superior to conventional cleaning but can only be used in enclosed rooms as it is toxic to humans. Interestingly, MRSA may not be completely cleared with a conventional solution containing 5–15% non-ionic surfactant and 5–15% cationic surfactant, diluted 1:500.


Guidelines exist for floor space in ICUs (see ESICM and SCCM references above). The transmission of micro-organisms will occur more readily in cramped conditions. There are recommendations for the number of isolation cubicles that should be available for patients with resistant organisms and for immunocompromised patients.

Routine ICU management

Meticulous adherence to simple infection control procedures within the ICU, such as hand washing, the removal of watches, removal of jackets and rolling up
sleeves, minimises the risk of organism transmission. Regular naso-pharyngeal suctioning and sitting the patient at an angle of 45° as part of a ‘ventilator bundle’ or guidance (see reference below) may reduce the risk of ventilator-associated pneumonia (VAP) likely by minimisation of micro aspiration. Continuous supra-glottal suction has recently been proposed as a means of reducing VAP. Rationalising the number of intravenous cannulae and the provision of written guidelines for their management may avoid the complications of catheter-related sepsis.


Guidelines

Check what written policies regarding infection control exist on your unit. Are there guidelines for the insertion and maintenance of central venous catheters? Do you consider them effective/appropriate? Discuss with your colleagues.

Antibiotic restriction/stewardship policies

The use of antibiotic policies and antibiotic rotation should be considered to help reduce the development of resistant bacteria within the ICU environment. ICU clinicians should work closely with their colleagues in Microbiology and Infectious Diseases to optimise appropriate and avoid inappropriate use of antibiotics. Hospital-based antibiotic stewardship programmes appear to improve the quality of, and curtail inappropriate, prescribing and are associated with reduced drug costs and bacterial resistance – see Lesprit and Brun-Buisson below. Although some infections such as endocarditis and osteomyelitis require a longer duration of antibiotic course e.g. six weeks, there is an attempt to regularise duration of antibiotic therapy for standard infections. Chastre et al compared an eight versus 15-day course of antibiotics for VAP and showed therapeutic equivalence. Many hospitals now use short antibiotic treatment courses; the Surviving Sepsis Guidelines recommend a seven-day course as the reference duration of antibiotic therapy.


Antimicrobial prophylaxis

Antibiotic prophylaxis presents a dilemma. On the one hand, our commitment to reducing exposure to antibiotics is compromised by their use. On the other hand, prophylaxis is almost certainly beneficial in some cases. Prophylaxis is usually limited to a single dose except in circumstances such as prolonged surgery (>2 hrs), major blood loss (>2 L) and certain special indications. Many guidelines recommend 24 hrs of perioperative prophylaxis for major surgery and this accounts for a proportion of ICU antibiotic use. Critical care staff need to be alert to stopping such courses of prophylaxis in accordance with local and national guidelines, an example of which can be found at http://www.sign.ac.uk

In the immunocompromised patient

Fluconazole in a moderate dose may also be of value for patients such as those with neutropenia, HIV or liver transplant recipients. Trimethoprim-sulfamethoxazole prophylaxis during certain immunosuppressive regimens has all but eliminated PCP as a complication. CMV prophylaxis can also be considered for patients at risk. HSV reactivation is common in severely neutropenic patients and the use of acyclovir is therefore recommended following bone marrow transplant.

THINK: Can the use of prophylactic antibiotic therapy be justified in an age of increasing bacterial resistance?

Selective decontamination of the digestive tract

Selective decontamination of the digestive tract (SDD) usually consists of a mixture of orally administered non-absorbable antimicrobials, sometimes combined with a low dose intravenous antibiotic. The relative contribution of the oral SDD paste compared with the intravenous component is uncertain.

Within the intensive care community opinion is polarised. Studies have suggested that nosocomial infections e.g. VAP (and mortality) may be reduced, at least in certain subgroups of critically ill patients. There is, however, a reluctance amongst some clinicians to introduce SDD to ICUs because of concern that in the long term and over a large number of ICUs, despite evidence to the contrary, SDD would select for resistant organisms.

Effects of selective decontamination of digestive tract on mortality and

van Saene HK, Petros AJ, Ramsay G, Baxby D. All great truths are iconoclastic: selective decontamination of the digestive tract moves from heresy to level 1 truth. Intensive Care Med 2003; 29(5): 677-690. Review. PMID 12687326


**Routine surveillance of immunocompromised patients – is it of value?**

Although routine microbiological surveillance of both patient and environment allows a profile of resistant organisms in the ICU to be described, studies have suggested that many of the organisms are innocent bystanders and not necessarily responsible for infection. The presence of resistant organisms in an ICU does not necessarily imply that a patient is colonised; the presence of an organism on the patient does not necessarily imply infection.

In mechanically ventilated patients, it is virtually impossible to avoid tracheal colonisation. VAP can be categorised as early-onset or late-onset although the distinction is not well defined. Early-onset VAP is usually caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*, whereas *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are often isolated in those with late-onset VAP. After 30 days of ventilation approximately 35% of patients will have distal airway colonisation. As a result, current antibiotic policy should be to introduce broad-spectrum antibiotic treatment initially and de-escalate to narrower spectrum agents once an infecting organism has been identified.
CONCLUSION

The management of patients with immunosuppression represents a significant challenge to the Intensivist and the full intensive care team. Many patients are therapeutically immune suppressed e.g. post transplantation and an understanding of the therapy and its benefits, risks and side-effects are important to practice in this environment. As our understanding of the mechanisms of immune suppression has developed and the clinical recognition of patients with compromised immunity has improved, we can hope for a corresponding reduction in mortality. Better laboratory tests to ‘quantify’ immunosuppression would be useful, but we are a long way from discovering a 'magic bullet' to improve immunocompetency.
SELF-ASSESSMENT QUESTIONS

EDIC-style Type K

1. In deciding on antimicrobial therapy for a febrile neutropenic patient:

A. Clinical examination is not of relevance as therapy is standardised
B. Clinical identification of a source of infection will guide therapy
C. Start with broad-spectrum therapy and narrow/focus the therapy when pathogen organism identified
D. If there is not a response to the antibacterial regimen within 48hrs, consider addition of antifungal therapy

2. Of these immunosuppressant drugs (used for transplant recipient patients), which are calcineurin inhibitors?

A. Cyclosporin
B. Mycophenalate
C. Tacrolimus
D. Azothiaprine

3. Qualitative markers of immunosuppression include the presence of:

A. Neutropenia
B. Lymphopenia
C. Hypogammaglobulinaemia
D. Thrombocytopenia

4. The broad classification of the host barriers to microbial invasion and infection includes:

A. The integument e.g. the skin
B. The innate immunity system
C. The adaptive immunity system
D. The toll-like receptor system

5. Re. Infection in the first two months after solid organ transplantation:

A. Tends to be caused by standard ICU bacterial/fungal pathogens
B. Transmission of bacterial infection with donor organ is a cause
C. Re-activation of host Herpes disease due to immune suppression is a cause
D. Nocardiasis is common
EDIC-style Type A

6. The following are true of the innate immune system EXCEPT:

A. Is capable of reacting to foreign antigen in the absence of previous exposure
B. Is a rapidly acting, non-specific first line of defence against invading organisms
C. Includes phagocytic cells and natural killer cells
D. Includes the complement system and the acute phase protein response
E. Its memory allows for an enhanced response to antigen re-exposure

7. Factors which would favour the addition of a glycopeptide to an antibiotic regimen include the following EXCEPT:

A. Known colonisation with MRSA
B. Blood cultures positive for Gram-positive organisms
C. Catheter- or device-related infection
D. Recent hospitalisation or period of residency in a nursing home
E. Suspicion that a urinary tract infection is the source of the sepsis

8. In assessing the risk of infection in an HIV positive patient, a CD4 count of 150–200 (x 10^6/L) predisposes to the following infections EXCEPT:

A. Tuberculosis
B. Bacterial pneumonia
C. Oral candidiasis
D. Cytomegalovirus infection
E. Kaposi’s sarcoma (due to human Herpes virus)

9. Which one of the following is FALSE regarding CMV infection in solid organ transplant patients?

A. Up to 50% of transplant recipients develop CMV disease
B. Likelihood of acquisition of CMV disease depends on the serological status of the donor and recipient
C. Occurs most commonly following transplantation with a sero-positive donor
D. Can induce graft dysfunction
E. Does not exacerbate immunosuppression
10. In immunocompromised patients, CMV characteristically induces a variety of conditions EXCEPT:

A. Fever and leukopenia  
B. Hepatitis  
C. Pneumonitis  
D. Colitis  
E. Myositis

11. Which of the following regarding antibiotic stewardship policies is FALSE?

A. They incorporate a practice of reviewing antibiotic prescriptions  
B. They are designed to encourage appropriate antibiotic therapy  
C. They aim to reduce emergence of bacterial multi-drug resistance  
D. They are associated with reduced hospital costs  
E. They have been shown to slow the implementation of timely antibiotic therapy

12. Which of the following is true of Fungal infections?

A. Are never found in patients with life-threatening burns  
B. Are an early infective complication of solid organ transplantation  
C. Are not a presenting feature of acute leukaemias  
D. Are never life-threatening  
E. Are never resistant to antifungal chemotherapy

13. Which is true of CARS (compensatory anti-inflammatory response syndrome)?

A. Is easy to measure  
B. Is caused by alteration to the patient’s commensal organisms  
C. Is of shorter duration than SIRS  
D. Is associated with anergy  
E. Occurs in all patients following severe illness

14. All of the following are true of Tacrolimus EXCEPT:

A. Affects neutrophil function  
B. Levels should be monitored daily  
C. Does not have an adverse effect on renal function  
D. Is available only as an enteral preparation  
E. Effects are enhanced by erythromycin

15. All of the following are true in neutropenic patients EXCEPT:

A. Severity is defined by the absolute neutrophil count  
B. Viral infection is uncommon  
C. Patient isolation is advised for profound neutropenia  
D. Antifungal medication is indicated for pyrexia of unknown origin (PUO) greater than 72 hours  
E. They usually die of their underlying disease in ICU rather than sepsis.
Self-Assessment answers

Type K

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Type A

Q6. Answer E is correct
Q7. Answer E is correct
Q8. Answer D is correct
Q9. Answer E is correct
Q10. Answer E is correct
Q11. Answer E is correct
Q12. Answer B is correct
Q13. Answer D is correct
Q14. Answer C is correct
Q15. Answer E is correct
PATIENT CHALLENGES

A 46-year-old male patient was admitted postoperatively to the ICU following a liver transplant. He had presented to the hepatology department three months earlier for assessment because of deteriorating liver function due to chronic hepatitis B infection. He had significant ascites and had been treated for episodes of spontaneous bacterial peritonitis. He was poorly nourished and hyponatraemic with impaired renal function.

The donor was a 66-year-old male who had died following a subarachnoid haemorrhage and had been in the ICU for seven days. On macroscopic examination, the liver was 'fatty' – a sign of borderline organ function but the decision was taken to proceed. The donor was CMV antigen positive. The operation was technically difficult and there was moderate blood loss.

Links to other modules
PACT module on Acute hepatic failure
PACT module on Organ donation and transplantation

On arrival in the ICU, the patient was mechanically ventilated and receiving inotropic support. His systolic blood pressure was 90 mmHg and he had a tachycardia of 120 bpm. He was anuric despite cardiac output optimisation and a bolus of frusemide (furosemide). He was on 60% oxygen and had a PaO₂ of 10.3 kPa (78 mmHg), a PaCO₂ of 5.4 kPa (41 mmHg) and pH 7.26. He had metabolic acidosis with a base deficit of –10.6 and a whole blood lactate of 6.3 mmol/l and was commenced on renal replacement therapy. The standard immunosuppression in the unit consisted of:
• Tacrolimus – a calcineurin inhibitor
• Azathioprine
• Corticosteroids – hydrocortisone in the initial postoperative period

Components of immune suppression in transplant patients
Immunosuppressive drugs

Links to other modules
PACT module on Homeostasis
PACT module on Acute renal failure

Q. What factors make this patient susceptible to infectious complications?

A. There are factors applicable to all patients following a liver transplant (mainly due to immunosuppressive drugs) and others relevant to the individual patient. Risk factors in this case include:
    • Recipient's chronic hepatitis B infection
    • Recipient's recurrent peritonitis and recurring antibiotic therapy
    • Recipient's renal function
Postoperative renal replacement therapy
Length of the operation
Amount of blood transfused
Donor’s age
Donor’s CMV status
Anticipated long ICU stay

**Learning Issues**

Infection following solid organ transplantation
Risk factors


**Note**
Sepsis is a leading cause of death following liver transplantation especially in the first three months. Overall the risk of infection in liver transplant recipients has been reported to be between 5 and 60% with an attributable mortality of 5–80%.

**Q.** What prophylactic medication would you prescribe for the patient to prevent infection in the postoperative period?

**A.** We can assume that the standard, institutional perioperative antibacterial prophylaxis for this operation has been given. Specific to the transplant, the patient has chronic hepatitis B infection and without postoperative preventative strategies all patients will reinfect their grafts. Current prophylactic strategies will include both the antiviral drug lamivudine and hepatitis B immunoglobulin (HBIG). Lamivudine is started before the transplant and the HBIG is started intra-operatively. Both drugs are then continued indefinitely. The graft came from a CMV positive donor and so there is an increased risk of CMV reactivation over the coming weeks. Some centres provide CMV prophylaxis routinely. This is usually started during the second month post transplant when the risk of CMV infection is highest. PCP prophylaxis (cotrimoxazole) will also need to be considered.

**Learning Issues**

Antimicrobial prophylaxis
Early versus late infection
Reinfection of the patient
Reinfection of the graft

Over the following few days his condition stabilised. He remained ventilated and anuric on continuous veno-venous haemofiltration (CVVH). Inotropic support was discontinued and the initial metabolic acidosis resolved but he was left with a persistently raised whole blood lactate of approximately 3 to 4 mmol/l and his international normalised ratio (INR) remained prolonged at about 2.0. These findings suggested early graft dysfunction. An ultrasound scan (USS) showed good flow to and from the new organ.

In high-risk patients with organ failure the chance of postoperative infection is high. Broad-spectrum antimicrobial prophylaxis (which may include antifungal cover) is often considered. The specific agents used vary between centres.

Links to other modules
PACT module on Organ donation and transplantation

Q. The nurses ask how long prophylactic antibiotics should be continued in this patient.

A. Adherence to standard principles/guidelines on prophylaxis and to institutional protocols is advised. However, there are no randomised controlled clinical trials comparing different prophylactic regimens or their duration in these patients. Local practice will dictate what regimens are used. It is unclear how long prophylactic antibiotics should be prescribed for and in an uncomplicated transplant three doses of standard peri-operative prophylaxis should be sufficient. Although contrary to the principles/guidelines on peri-operative antibiotic prophylaxis, there is sometimes a reluctance to stop antibiotics in the early postoperative period – the ostensible hope being a reduction in the risks of infectious complications.

Epidemiological data regarding the timing of infections following transplantation can be useful in providing a rationale for treatment.

Timing of infections

This patient's antibiotics were stopped in this instance on the second postoperative day. An antifungal in prophylactic dosage and prophylaxis for PCP and hepatitis B were continued.
A new intern questions whether selective decontamination of the digestive tract (SDD) might be appropriate for this patient.

**Learning Issues**

*Selective decontamination of the digestive tract*

**Q. Is there a role for SDD in this patient? Give your reasons.**

**A.** Some transplant centres use SDD routinely in postoperative transplant recipients and reports suggest a reduction in the incidence of Gram-negative infections. The data, however, are uncontrolled. Controlled studies of the use of SDD have shown a reduction in infectious complications but were largely underpowered for mortality. Meta-analysis of trials of SDD has shown a reduction in the incidence of both infectious morbidity and mortality in some categories of patients. Trials including liver transplant recipients were excluded from the analysis, however, making it difficult to resolve the issue with the available data. Despite the level of evidence supporting SDD, the reluctance of many institutions to use it is that SDD is considered, despite evidence to the contrary, to intrinsically pre-dispose to the emergence of resistant organisms.

SDD is not part of this institution’s perioperative protocol and it is decided that it should not be given to this patient.

On the fifth postoperative day it was noted that the patient’s temperature had risen to 39 °C. Early morning blood samples had shown an unexpected increase in his white cell count and liver enzymes.

**Learning Issues**

*Fever in the neutropenic patient*

**Q. What further actions and investigations would you do now?**

**A.** Differentiation between an infective and non-infective cause can be difficult and involves clinical examination and ancillary testing. Infection is likely and a search for the source should be undertaken. Cultures from blood, sputum and drain fluid, if available, should be performed. Serial CRP measurements may be of some assistance. Abdominal examination may suggest the abdomen as a source of sepsis; look for loss of bowel sounds and distension. Serum amylase may be helpful if pancreatitis is suspected. A chest X-ray may show pulmonary infiltrates suggestive of infection. A USS or CT scan looking for an intra-abdominal collection may be performed and evidence of pancreatitis may be suggested. A Doppler USS is also the initial investigation used to rule out vascular complications at this stage followed by angiography for confirmation. If acute rejection is suspected a liver biopsy is indicated.
The chest X-ray showed some left lower lobe collapse but had not changed significantly from the previous day. As there is not an evident source of infection, catheter-related sepsis is suspected and his CVCs and arterial catheters were removed (tips were sent for culture) and re-sited. Blood cultures were sent for microbiological analysis as part of the septic work-up. An urgent ultrasound scan failed to show any vascular insufficiency and so a liver biopsy was performed.

You meet with the patient's family to explain the deterioration in his condition.

Q. While waiting for the biopsy report what blood tests are available to help distinguish between rejection and infection?

A. The eosinophil count is often high in acute rejection. Procalcitonin is an acute phase protein that is raised in infection but not in acute rejection episodes and may have a role in post transplant surveillance.

The biopsy report suggested moderate to severe acute rejection. The patient was started on a three day course of high-dose steroids and the calcineurin inhibitor dose was increased.

Q. Do you think acute rejection increases the risk of infectious complications? What is the mechanism?

A. Yes. An acute rejection exacerbates immunosuppression and will therefore increase the risk of infection.

**Learning Issues**

*Mechanisms of immunosuppression*

Despite the increase in immunosuppression the patient’s temperature remained high and his white cell count continued to climb.

Q. What are your therapeutic actions at this stage?

A. Even without confirmatory microbiological data, the evidence for infection is strong despite the biopsy report showing evidence of acute rejection. You should start the patient on antibiotics for a presumed infected collection in the subhepatic space.

**Note** There are often multiple problems in immunocompromised patients – a high index of suspicion is required. Infection and rejection often occur simultaneously.

After the septic work-up, the patient was started on a broad-spectrum antibiotic. Meropenem (a broad-spectrum, carbopenem) was used and reviewed when culture results were available. The extended septic work-up included a CT scan of his abdomen which revealed a collection around the porta hepatis. A drain was placed by an interventional radiologist and brown fluid was aspirated which was sent for Gram-stain and culture.

**Learning Issues**

*Early antibiotic therapy for severe sepsis*  
*Source control for sepsis*

**Links to other module**  
PACT module on Sepsis and MODS
Q. At this stage what are the most likely sites of infection and what organisms are likely to be involved?

**Prompt:** Solid organ transplant recipients tend to develop infections related to the transplanted organ, e.g. biliary infections following liver transplants, pneumonia following lung transplant and urinary tract infections following renal transplantation.

A. Infections that occur within the first month following solid organ transplantation are similar to infections seen in other non-immunocompromised surgical patients. The same sites and organisms are responsible, including wound infections, pneumonia, catheter-related blood stream infections and urinary tract infections. The causative organisms include Gram-negative followed by resistant Gram-negative and Gram-positive organisms including MRSA. Later vancomycin-resistant enterococci, fungi and *Clostridium difficile* infections become prevalent.


**Learning issues**

Infections up to one month

The following day, cultures from the subhepatic space grew a mixed flora of aerobic Gram-negative organisms and meropenem was continued. The patient’s condition improved over the next few days but he remained ventilated and in anuric renal failure requiring CVVH.

A tracheostomy was performed. His sedation was stopped. He became more alert and he began to pass urine. He was able to wean from ventilation and was ready for transfer to an HDU on a T-piece with FiO₂ of 0.4 over the next 2–3 days. As he was swallowing well, his tracheostomy cuff was deflated allowing him to communicate via a speaking valve. His abdomen was soft, bowel activity recommenced and full enteral nutrition was maintained via a nasogastic tube. Intravenous antibiotic therapy (meropenem) was stopped and he was prepared for transfer to the Liver ward some days later on maintenance immunosuppressive therapy and on the ongoing antimicrobial prophylaxis as outlined above.
A 37-year-old male was admitted to the ICU eight days after an allogeneic stem cell transplant. He had been treated with chemotherapy three months earlier for relapsed acute myeloid leukaemia and had achieved complete remission. He was blood group A Rh (D) positive and serology showed him to be CMV seropositive.

**Causes of immune suppression**

The donor for the transplant was an HLA-identical unrelated 28-year-old female who had had three pregnancies. She was blood group A Rh (D) positive and CMV seronegative.

Conditioning for the transplant was myeloablative with total body irradiation (14.4 Gy given in 8 fractions) and high dose cyclophosphamide (60 mg/kg per day for two days). Antimicrobial prophylaxis was with oral ciprofloxacin 500 mg twice a day. Stem cell reinfusion occurred uneventfully. Cyclosporin A and methotrexate were used as prophylaxis against graft versus host disease.

**Graft versus host disease**

Conditioning is the process used to ablate the host bone marrow and immune system. In patients over the age of 50 years, ‘reduced intensity’ approaches are used, primarily targeting the host immune system.

On day six after the transplant, the patient developed a fever of 38.5 °C but remained normotensive and maintained a urine output of >50 ml/hr. Blood cultures were taken simultaneously from the tunneled central venous catheter (CVC) and peripherally. Throat swab and urine samples were sent for microbiological culture.

**Fever in the transplant patient**

Antibiotic therapy with gentamicin and piperacillin/tazobactam was commenced. Blood tests showed a total white cell count of 0.1 x 10⁶/l and a C-reactive protein of 14 mg/l. The following day, the patient was still febrile and the CRP had risen to 85 mg/l. On the day of ICU admission, the patient had deteriorated, with a systolic blood pressure of 67 mmHg, O₂ saturations of 86% on 5L O₂ by mask and oliguria. Arterial blood gas analysis showed a pH of 7.24, a pO₂ of 8.8 kPa (66 mmHg) and whole blood lactate was raised at 4.28 mmol/l. Both sets of blood
cultures demonstrated a coliform organism resistant to ciprofloxacin, gentamicin and piperacillin/tazobactam but sensitive to meropenem. The sample from the tunneled CVC became positive four hours before the peripheral blood culture – suggesting catheter-related infection.

**Learning Issues**

*Suspicion/diagnosis of catheter-related infection*

*Infection in the transplant patient*

**Links to other module**

PACT module on Pyrexia
PACT module on Sepsis and MODS

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**Q.** Which factors make this patient susceptible to infection?

**A.** Risk factors
   - Malignancy
   - Prior chemotherapy
   - Stem cell transplant conditioning and neutropenia
   - Immunosuppressive drugs (cyclosporin/methotrexate)

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**Q.** What are your therapeutic actions at this stage?

**A.** Maintenance of the meropenem (for GNB therapy pending knowledge of full antibiogram picture), continuance of resuscitative/organ supportive measure e.g. inotropic support and removal of the source of infection – the tunneled CVC.

Respiratory function improved and mechanical ventilation was not required. One day later, body temperature had fallen to 37.4 °C and systolic blood pressure was 105 mmHg on inotropes. However, the patient had developed diarrhoea. Over the following 36 hours, the volume of diarrhoea increased to 2.8L/24 hours.

**Q.** What are the possible causes of diarrhoea in this case?

**A.** Infectious e.g. *C. difficile* and non-infectious e.g. inter-current antibiotic therapy, earlier laxative therapy, enteral feed intolerance, graft versus host disease.

Testing for *Clostridium difficile* toxin was negative and culture demonstrated no significant pathogens. Colonoscopy and biopsy were performed and biopsy was reported as consistent with graft versus host disease.

**Q.** Which factors make this patient more likely to develop acute graft versus host disease?
A. Unrelated donor, parous female donor, sex mismatch between recipient and donor.

Treatment with intravenous methylprednisolone 1 mg/kg twice daily was commenced with a reduction in stool volume 48 hours later. The patient returned to the ward.

**Learning Issues**

*Immunosuppressive (booster) therapy*

72 hours after returning to the ward, the patient’s respiratory function deteriorated, with $O_2$ saturations of 88% on 15L $O_2$ by mask, respiratory rate of 36/minute and an inability to speak in sentences. He was normotensive and urine output was >50 mls/hour. He was readmitted to the ICU and shortly after admission was intubated and mechanical ventilation commenced for respiratory distress, obtundation and hypoxaemia. He was noted to have a temperature of 38.2°C. Neutrophil count was $0.3 \times 10^9/l$.

**Q. What pathogens need to be considered under these circumstances?**

A. Bacterial; viral – CMV, RSV, influenza A/B, H1N1, zoster; fungal including PCP.

**Q. What non-infectious causes could result in an acute clinical deterioration such as this?**

A. Pulmonary oedema from fluid overload.
Idiopathic pneumonitis (including alveolar haemorrhage).
ALI/ARDS due to chemoradiotherapy.

**Q. What further investigations would you request/organise?**

A. Blood cultures.
Peripheral blood PCR for CMV.
Bronchoalveolar lavage, sending samples for viral PCR (CMV, influenza A/B, RSV, H1N1), fungal staining and culture, PCR for PCP.
Imaging including CXR and HRCT of chest when stable.

After septic work-up, treatment was commenced with meropenem, liposomal amphotericin, cotrimoxazole and ganciclovir. After 36 hours, PCR on peripheral blood had shown the presence of CMV (360,000 copies/ml of blood) and also was positive for CMV (qualitative assay) in bronchoalveolar lavage fluid.

**Q. What are the risk factors for CMV pneumonitis?**
A. Highest risk – CMV positive recipient and CMV negative donor.  
The use of CMV positive blood products.  
The use of high dose steroids for graft versus host disease.  
The use of immunosuppressive agents such as cyclosporin A.  
Recipient age (frequency increases with increasing age).

There was no apparent response to initial therapy and the patient remained on mechanical ventilation for a further 12 days. Despite supportive and specific therapy (intravenous ganciclovir and immunoglobulin) the overall course was downhill. Ventilation became more difficult and support was changed to an oscillating ventilator.

Links to other modules  
PACT module on Respiratory failure  
PACT module on Mechanical ventilation

No improvement was seen and CXR infiltrates became progressively worse despite above specific and supportive therapies. The view of the Critical Care and the visiting medical teams was that all reasonable medical measures had been implemented and that the patient was not responding. The consensus view at senior level was that the life-sustaining measures were now futile for this patient.

Links to other modules  
PACT module on Ethics

Q. How would you approach the care of this patient? What would you say to his next of kin?

A. The family are told at serial meetings of the patient's worsening and poor prognosis. The family's view on what the wishes and disposition of the patient to this form of invasive therapy will have been explored at these meetings. The focus of care may have to change now to keeping the patient comfortable by palliative means and indeed managing his death in an appropriate manner. After the multidisciplinary meeting at which consensus is reached, a family conference is held where the grave prognosis of non-responsive CMV pneumonitis in stem cell transplant is reiterated, the futility of the current invasive measures is explained and the recommendation to change to palliative care is made. Often, by the time this is apparent to medical staff, families already have reached the conclusion that the treatments are disproportionately burdensome and readily accept this recommendation and approach. Measures are then taken to limit/stop (withdraw) the invasive interventions, ensure comfort and allow the patient to die peacefully, without medical disturbance, in the presence of his family.
On reflection, complications are common following solid organ and stem cell transplantation. Transplant physicians quote procedural mortality of 10–20% following stem cell transplantation.

A complicated post-operative course and the treatment of graft versus host disease increase the risk of infections. A high index of suspicion is required. Infection is the major early cause of morbidity and mortality, and infection can of course occur despite the use of appropriate antimicrobial prophylaxis.

The first patient was high risk because of his multiple comorbidities and this was compounded when he received a suboptimal graft. Aggressive early investigation to differentiate infection from rejection (or whether both co-exist) is required. Prompt appropriate treatment is required as it is known to improve survival, particularly in severe sepsis and septic shock. If therapy is unsuccessful, as in the case of the second patient, it is important that this be recognised at a senior level and a consensus view on palliation be reached where appropriate.

Communication with the family is very important, should start early and be ongoing.