Respiratory infections following haemopoietic stem cell transplantation in children

Paul Veys* and Catherine Owens†
*Bone Marrow Transplant Unit and †Department of Diagnostic Radiology, Great Ormond Street Hospital for Children NHS Trust, London, UK

Disorders of the respiratory system are well recognised following the administration of chemotherapy schedules; although respiratory complications may occur following less intensive regimens, they are most frequently seen following the administration of high dose chemotherapy with or without radiotherapy which is used in preparation for haemopoietic stem cell transplantation (SCT). In this setting, respiratory complications may occur in up to 50% of patients and account for over 40% of all deaths1,2; those patients who require admission to intensive care (ICU) requiring intubation and mechanical ventilation have a particularly poor prognosis1,3,4, with less than 10% becoming long-term survivors.

For over 30 years, SCT has been used to cure children with a wide spectrum of diseases including high-risk and relapsed leukaemia, solid tumours, haemoglobinopathies, immunodeficiencies and a variety of metabolic disorders. Between 300–350 SCTs are performed on children each year in the UK – 80% are from allogeneic (non-self) donors using stem cells from bone marrow, umbilical cord blood, or G-CSF mobilised peripheral blood progenitor cells (PBPCs), and 20% are autologous

Table 1 Respiratory complications following haemopoietic stem cell transplantation (SCT)

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<tr>
<th>NON-INFECTIONOUS</th>
<th>INFECTIONOUS</th>
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<tr>
<td>Airway</td>
<td>Bacterial</td>
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<td>Mucositis</td>
<td>Cytomegalovirus (CMV)</td>
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<td>Parenchyma</td>
<td>Viral</td>
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<td>Idiopathic pneumonia syndrome (IPS)</td>
<td>Respiratory syncytial virus (RSV)</td>
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<td>Diffuse alveolar haemorrhage (DAH)</td>
<td>Adenovirus</td>
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<td>Pulmonary oedema</td>
<td>Parainfluenza</td>
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<td>Graft versus host disease (GvHD)</td>
<td>Human herpes virus (HHV6)</td>
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<tr>
<td>Pulmonary vascular disease</td>
<td>Other</td>
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<tr>
<td>Pulmonary embolism</td>
<td>Fungal</td>
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<tr>
<td>Pulmonary veno-occlusive disease (VOD)</td>
<td>Aspergillus</td>
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<td>Candida</td>
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<td>Other</td>
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<td>Pneumocystis carinii (PCP)</td>
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<td>Mycobacterial</td>
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(self) transplants, utilising predominantly PBPCs and performed mainly for paediatric solid tumours.

Respiratory complications following SCT are listed in Table 1, and may be divided into two broad categories based on the presence or absence of infection. This chapter will discuss the respiratory infections complicating SCT, but will also address non-infectious complications where an infectious agent may be part of a poorly understood pathogenesis.

Children undergoing SCT require intensive immunosuppressive and/or myelo-ablative chemotherapy which causes a profound pancytopenia in combination with severe combined immune deficiency with suppression of both cell-mediated (T-cell) and humoral (B-cell) defences. As well as depressing the systemic defence mechanisms, a number of local lung defences are compromised by the SCT procedure.

**Local lung defences**

Micro-organisms that enter the airways between the larynx and the respiratory bronchioles are coated with secretory IgA, which inhibits adherence to the respiratory epithelium. These micro-organisms are then expelled by mucociliary transport; microbes that evade these first lines of defence and reach the alveoli are then ingested by alveolar macrophages. These macrophages release several cytokines including tumour necrosis factor (TNF), IL-1 and IL-8, which, in turn, stimulate the release of additional cytokines by epithelial cells, endothelial cells and fibroblasts. Together, these mediators recruit circulating neutrophils into the alveolar spaces. This neutrophil influx is essential for eradication of bacteria and fungi, particularly *Candida* and *Aspergillus*.

The combination of mucositis and global suppression of the body’s cellular defences by chemotherapy means that these local defence mechanisms are severely impaired following SCT.

**Recovery of the immune system**

Re-population of the lung by donor-derived alveolar macrophages does not occur for several weeks after SCT; macrophage function may remain impaired for several months\(^5\). Recovery of neutrophil counts in the peripheral blood usually occurs within 2–3 weeks. It is typically more rapid following the use of mobilised PBPCs rather than bone marrow stem cells\(^6\), but may be delayed by myelosuppressive drugs including methotrexate, septrin and ganciclovir. Recovery of lymphocyte counts is more prolonged, with numbers usually approaching the normal range within 3 months of transplantation, but T cell function and response to allo-antigens may not return for at least 6 months after SCT. T-cell recovery is significantly prolonged following HLA
mis-matched transplantation particularly until T-cell depletion of the graft has
been performed to reduce graft versus host disease (GvHD). Return of B-cell
function and humoral antibody production may take up to a year. Immune
reconstitution is also prolonged in the presence of GvHD and its requirement
for on-going immunosuppressive therapy

The temporal sequence of immunological recovery determines the
predisposition of the child to respiratory infections at any given time point.
The post-transplantation period can be divided into two risk periods.
During the pre-engraftment period, patients are most susceptible to
bacterial infections and specific viral infections. After neutrophil recovery,
T- and B-cell-mediated immunity remains abnormal, predisposing the
patient to infection with viruses, fungi, mycobacteria, and parasites. The
impaired synthesis of immunoglobulins including excretory IgA prolong
the patient’s susceptibility to bacterial pneumonias (Fig. 1).

Fig. 1 Approximate time of onset of respiratory disorders in the first 4 months after SCT.
DAH, diffuse alveolar haemorrhage; VOD, veno-occlusive disease; HSV, herpes simplex virus;
RSV, respiratory syncytial virus; IPS, idiopathic pneumonia syndrome; GvHD, graft versus host
disease; CMV, cytomegalovirus; PCP, Pneumocystis carinii pneumonia; dotted line, risk of
bacterial pneumonia continues due to impaired synthesis of immunoglobulins.
Specific infections

Most of the published studies regarding respiratory infections following SCT relate largely to adult practice, very few studies have been performed solely in children. While the spectrum of disease occurring in both adults and children is the same, the true incidence of many of these infections following paediatric SCT remains uncertain, although it is thought to be somewhat lower in the paediatric population. One of the reasons for this may be the reduced incidence of GvHD following SCT in children compared to adults, probably as a result of persisting thymic function in childhood; the occurrence of GvHD and its treatment is closely related to an increased susceptibility to infection. A study performed at the Children’s Hospital in Munich between 1975–1999 reported respiratory complications amongst 150 SCTs performed on 138 paediatric patients suffering from non-malignant diseases; 17 patients had severe respiratory complications. Early severe respiratory complications leading to death in the first 4 months after SCT were due to infection in 6 (4%; fungal pneumonia [3], bacterial pneumonia [1], and viral pneumonia [2]). In Houston between 1992–1996, there were 10 viral pneumonias amongst 96 children undergoing SCT, which were fatal in 6 (6%; Table 2).

The authors have retrospectively studied 450 consecutive paediatric SCTs at their own institution (GOSH) performed during 1990–2000 (Table 2). There were 164 deaths in this patient cohort, 92 due to disease relapse, 72 non-relapse deaths, 69 (15%) in which respiratory failure was a major component. Of the 69, 28 (6%) were due to respiratory infection.

Table 2 Respiratory paediatric infections undergoing SCT at GOSH in London (1990–2000), MD Anderson Cancer Center in Houston (1982–1986), and Children’s Hospital, Munich (1975–1999)

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<td>Patients (n)</td>
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<td>London</td>
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<td>Bacterial</td>
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<td>450</td>
<td>96</td>
<td>150</td>
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<td>(ARDS associated with bacterial sepsis)</td>
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<tr>
<td>Viral</td>
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<tr>
<td>Cytomegalovirus (CMV)</td>
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<td>4 (4)</td>
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<tr>
<td>Respiratory syncytial virus (RSV)</td>
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<td>Adenovirus</td>
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<td>Herpes simplex virus (HSV)</td>
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<td>Epstein-Barr virus (EBV)</td>
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<td>Lymphoproliferative disease (LPD)</td>
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<td>Influenza</td>
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<td>Fungal</td>
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<td>9 (2)</td>
<td>8(2)</td>
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<td>Aspergillus</td>
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<td>Pneumocystis carini pneumonia (PCP)</td>
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13 (3%) due to ARDS associated with bacterial sepsis, and 28 (6%) were regimen-related toxicity. Hence all 3 studies point to a mortality rate from respiratory infection following paediatric SCT of between 4–6%.

**Bacterial infections**

Bacterial pneumonia may occur in as many as 10% of patients during the pre-engraftment period, and has been associated with a high mortality\(^1\). Pneumonia may be caused by the direct spread of organisms from the oropharynx following impairment of local defences, but may also be produced by septic emboli originating from an in-dwelling intravenous catheter or through damaged mucosa in the gastrointestinal tract. Some 90% of bacterial infections occur when the neutrophil counts are below 0.1 \(\times 10^9/l\). Gram-negative bacteria are the most virulent bacterial pathogens during neutropenia and historically have been the major causes of morbidity and mortality. Gram-negative bacilli causing bacterial pneumonia include *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Enterobacter cloacae*. More recently, Gram-positive bacteria have emerged as major pathogens; bacteraemia rates for Gram-positive organisms now exceeds that of Gram-negative bacteria\(^{10}\). This increase is in large part due to the near universal use of in-dwelling venous catheters. The most common Gram-positive organism causing bacterial pneumonia is *Staphylococcus aureus*, although also of note are the \(\alpha\)-haemolytic streptococci (e.g. *Streptococcus mitis*) which are thought to gain entry through damaged oral mucosa and are associated with a toxic shock-like syndrome with an adult respiratory distress syndrome (ARDS) type picture in 10% of cases\(^{11}\). Anaerobic pneumonia may also occur, especially in patients with severe mucositis and recurrent aspiration. In addition, a number of centres have reported outbreaks of pneumonia due to *Legionella pneumophila*\(^{12}\). During the postengraftment period, patients remain at risk of bacterial infections because of continuing impairment of humoral immunity. Pneumonia during this period is caused primarily by encapsulated organisms, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*, and patients require prophylaxis with penicillin, and vaccination against both organisms from 1 year post-SCT.

Patients usually present with cough, fever, dyspnoea and reduced oxygen saturation. A chest X-ray usually demonstrates one or more patches of consolidation which may progress to a more diffuse picture. Septic emboli typically appear as poorly defined peripheral nodules. These may cavitate and be associated with pleural effusion. Peripheral cavitating nodules may also be seen in aspergillosis, which becomes an important differential diagnosis. In practice, making a diagnosis of bacterial pneumonia is often difficult because of the large number of alternative diagnoses in this patient group, the frequent use of empiric broad-spectrum antibiotics,
and the inaccuracy of commonly used diagnostic tests. Blood cultures are often negative in patients with bacterial pneumonia, and bacteraemia when present often originates from sites other than the lung. Improved diagnostic specificity may be achieved by sampling distal airways and alveoli using techniques such as broncho-alveolar lavage (BAL). For these reasons, it was difficult to give an accurate number of true bacterial pneumonias in the population study at GOSH (Table 2), and in only 1 case was bacterial pneumonia identified as the cause of death. Conversely, ARDS associated with generalised bacterial sepsis was the major cause of mortality in 13 (2.9%) patients. The treatment for bacterial pneumonia is often empiric and a combination of an aminoglycoside and anti-pseudomonal penicillin is usually given to provide coverage against both Gram-negative bacilli as well as Gram-positive organisms. Vancomycin or teicoplanin are frequently added if a Gram-positive organism is confirmed, and azithromycin if an atypical organism is suspected.

**Viral infections**

**Cytomegalovirus**

Infection with cytomegalovirus (CMV) used to account for approximately 40% of all pneumonias occurring after SCT. A large series reported incidence rates ranging from 10–20% in allogeneic SCT and 1–4% in recipients of autologous transplants. Acquisition of CMV may be via primary infection from donor cells or blood products in a previously seronegative patient, re-activation of endogenous virus, or re-infection with a different strain of CMV in a previously seropositive patient. With the introduction of CMV-negative and/or filtered blood products, the most likely source in practice is re-activation of endogenous virus, either from a seropositive recipient or donor. A combination of reduced prevalence of CMV in children and their childhood donors and better recent prophylaxis for CMV during the at-risk period has reduced the incidence of CMV pneumonitis in the paediatric SCT setting; 9/450 (2%) patients at GOSH developed probable CMV-pneumonitis during their transplant episodes. Most cases of CMV pneumonia occur after marrow engraftment during the first 100 days of transplantation, and almost all within 180 days. With the more recent successful prophylaxis of CMV during the early post-SCT period, there has been a resurgence of late CMV infection occurring beyond the first 100 days. CMV pneumonia is very uncommon prior to marrow engraftment. In the setting of a seropositive child or donor, additional risk factors for occurrence of CMV re-activation/disease include higher pretransplant total doses of total body irradiation (TBI) and chemotherapy, presence and severity of acute GvHD and the use of intensive T-cell depletion strategies.
Fig. 2  (A) Portable AP supine chest X-ray showing mild overinflation of the lungs in a child who is not intubated. There is diffuse granular shadowing throughout all zones of the lungs consistent with interstitial pneumonitis caused by cytomegalovirus (CMV).

(B) Extensive interstitial pneumonitis with a complicating right sided pneumothorax and air tracking around the lung, in a subpulmonic distribution and into the anterior pleural reflection on the right side. The pneumothorax persists despite the presence of right basal chest drain. The appearances are of diffuse disseminated CMV pneumonitis with complicating baro-trauma induced lung disease and air leak.
Clinical manifestations of CMV pneumonia are not specific and include non-productive cough, fever, progressive dyspnoea and hypoxaemia. Chest X-ray typically shows diffuse interstitial alveolar infiltrates (Fig. 2A,B), and numerous small nodules may be evident on CT\textsuperscript{20}.

CMV pneumonia is usually diagnosed by detection of virus in BAL fluid. Monoclonal antibodies can rapidly detect the presence of CMV antigen within infected cells, and typical CMV inclusions maybe evident by histological examination. Recently, DNA amplification using the polymerase chain reaction (PCR) has been shown to be a very sensitive method for detecting CMV\textsuperscript{21}. CMV may be isolated from the lower respiratory tract of both immunocompetent and immunocompromised children in the absence of pneumonia; hence, detection of virus in respiratory samples does not necessarily establish a diagnosis of CMV pneumonia. Nevertheless, CMV must always be considered a pathogen in patients undergoing SCT, and CMV in pneumonia should be diagnosed in any patient with compatible clinical findings.

The best therapeutic regimen consists of combination therapy with intravenous ganciclovir and immune globulin (either CMV specific or pooled). However, although this approach has been shown to decrease mortality significantly, response rates may be as low as 35\% and mortality rates in patients requiring mechanical ventilation continues to approach 100\%\textsuperscript{22}. Consequently, approaches designed to prevent CMV pneumonia are essential in the management of patients undergoing SCT. In seronegative patients, the best approach is to transplant stem cells and transfuse blood products from seronegative donors\textsuperscript{23}. Leukodepleted products may be used in an emergency if no CMV-negative blood products are available. In seropositive patients and seronegative patients who received a transplant from a seropositive donor, prophylactic administration of immunoglobulin and high-dose acyclovir therapy\textsuperscript{24} is the most widely used regimen in paediatrics at the present time. In patients at risk of CMV infection, the viral load is monitored weekly with PCR methods and a rising titre is treated promptly with ganciclovir\textsuperscript{25}. If therapy with ganciclovir is not successful in reducing the viral load or indeed causes excess myelo-suppression, it may be substituted for foscarnet or indeed a combination of 50\% of both drugs is currently being assessed.

Further studies are also underway to assess the efficacy of CMV specific cytotoxic T-cells which have been generated in vivo using donor T-cells. At the present time, it seems most appropriate to use such technology in patients in whom CMV loads are rising despite therapy with ganciclovir or foscarnet.

\textbf{Respiratory syncytial virus (RSV)}

RSV is a common cause of respiratory tract infections in infants and children. Although RSV may be confined to upper respiratory tracts in
SCT, it not infrequently leads to a devastating primary viral pneumonia. The true incidence of RSV pneumonia in SCT is unknown, although figures as high as 11% have been suggested\textsuperscript{26}. At GOSH, there were 7 cases in 450 (1.6%) transplanted patients. RSV pneumonia is most common in the very early period after transplantation during the pre-engraftment period. In most cases, pneumonia occurs in the spring and winter months and is usually preceded by the symptoms and signs of rhinitis. Chest X-ray initially shows diffuse infiltrates and progression to diffuse air space disease is common (Fig. 3). Despite antiviral therapy, RSV pneumonia is associated with a high mortality rate of around 50\%\textsuperscript{27}. A diagnosis of RSV is usually made by detection of RSV antigens within infected cells from a nasopharyngeal (NPA) or from BAL fluid using fluorescent monoclonal antibodies. In view of the high mortality rate, therapy should be started as soon as RSV is isolated from the upper respiratory tract during the transplant course. Appropriate therapy
consists of nebulised +/- intravenous ribavirin and RSV-specific hyper-immune globulin/intravenous immunoglobulin. Better still, if RSV can be detected prior to SCT in an NPA, it is prudent to defer the procedure if at all possible. RSV is highly contagious and may spread rapidly throughout the transplant unit. Aggressive policies for prevention of nosocomial infection is paramount and may reduce the incidence of RSV disease during outbreaks in transplant units.

**Adenoviruses**

Members of this virus group are common causes of respiratory and gastrointestinal illnesses in children. Re-activation of latent virus or primary infection has now been widely described after SCT, both during the neutropenic period and postengraftment. Serotypes belonging to subgroups B and C are most commonly isolated. Incidental detection in the stool of an asymptomatic patient is becoming increasingly common with the institution of specific screening. In some patients undergoing SCT, gastrointestinal infection may lead to severe diarrhoea which must be rapidly differentiated from gastrointestinal GvHD as steroid therapy may exacerbate adenoviral infection. Some of these children will go on to develop disseminated adenoviral infection which may be suspected by the detection of adenovirus in the peripheral blood using PCR techniques. Within a variable period extending from days to several weeks, some of these children will develop rapidly fatal forms of hepatitis often accompanied by pneumonitis (Fig. 4A–C). Progression from asymptomatic excretion to fulminant fatal infection is exacerbated by profound T-cell depletion of the graft and ongoing immunosuppressive therapy particularly with high doses of steroids. This is, therefore, most frequently seen in the setting of mismatched SCT, particularly haplotype mismatched transplants.

Analysis of 206 consecutive patients undergoing SCT at St Jude’s Children’s Research Hospital between November 1990 and December 1994 identified 13 (6%) patients with adenovirus infection. Adenovirus was first detected at a median of 54 days and occurred in 11.6% of patients undergoing unrelated or mismatched related, 7.7% HLA matched siblings, and only 1.1% of patients receiving autografts; 4 patients had an associated pneumonitis and in 2 (1%) cases this proved to be fatal. As well as type of bone marrow graft, use of total body irradiation in the preparatory regimen was a significant risk factor; 6 (1.3%) of the GOSH patients had an adenoviral pneumonitis, and this was fatal in 4 (0.9%) of these.

There are currently two antiviral drugs which show some promise in the setting of adenoviral infection, namely ribavirin and cidofovir. However, both of these drugs are only virustatic and neither of these therapies is effective in fulminant disease, but may be useful in the early stages of disseminated infection when PCR for adenovirus first becomes positive in the peripheral blood.
Parainfluenza virus (PIV)

PIV is a common respiratory pathogen in children. The commonest serotype seen in the UK is PIV-3, which has been observed to have an annual ‘summer epidemic’ pattern of occurrence. Following SCT, there have been only two large retrospective studies\textsuperscript{32,33}, both including largely adult patients. In this group of patients, the incidence of PIV infection

\begin{figure}[h]
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\caption{(A) Portable AP supine chest radiograph and (B) corresponding CT showing diffuse ground glass shadowing throughout both lungs, more marked in the right lung with marginal overinflation of the lungs in an intubated patient due to adenoviral bronchiolitis. (C) Abdominal radiograph shows diffuse pneumatosis intestinalis related to adenoviral gut infection. Tubular lucencies are seen in the wall of the colon related to gas within the colonic wall. There is no evidence of perforation on the radiograph.}
\end{figure}
was between 2.5–5%. A lower respiratory tract infection developed in half of these patients, and mortality was 33%, underlying the threat that PIV presents to SCT patients. Ribavirin may be an effective treatment, particularly if started early in the course of infection. Patients who are asymptomatic or only mildly symptomatic may respond to oral ribavirin doses of 60 mg/kg/day. In those with more severe symptoms, it is preferable to give aerosoled ribavirin 6 g/day in 3 divided doses. Patients diagnosed with probable definite lower respiratory tract infection should probably receive intravenous ribavirin. Aerosoled ribavirin is usually associated with little treatment-related toxicity, but high dose oral or i.v. administration may be associated with reversible anaemia. PIV infection may occur during the pre- or postengraftment periods.

**Herpes simplex virus (HSV)**

HSV pneumonia following SCT is rare, presumably due to routine use of prophylactic acyclovir in most patients. In all reported cases of pneumonia, it was preceded by mucocutaneous infection, usually from contiguous although very occasionally from haematogenous spread of infection. In most patients, HSV pneumonia is associated with progressive respiratory failure and a very high mortality rate.

**Influenza**

Influenza virus continues to cause annual epidemics of respiratory disease which are associated with substantial morbidity and mortality, particularly amongst people with underlying health problems. Public health policies recommend annual influenza vaccination for all immunosuppressed patients, their families and hospital staff. Recognising that many of the immunosuppressed patients will not develop an adequate antibody response to vaccine, there had been recommendations that prophylaxis with amantadine 'may be indicated' for the duration of any influenza A epidemic in the community. In Houston, Texas, the 1991–1992 influenza epidemic extended from 6 weeks in the middle of November to the middle of December. During this period, 68 adult BMT recipients were monitored for respiratory illness. Influenza virus type A was isolated from 8 of 28 BMT recipients (29%) who had an acute respiratory illness. Five of these infections were acquired in hospital. All 8 patients presented with an upper respiratory tract illness, and in 6 patients the infection was complicated by pneumonia. The frequency of influenza was similar amongst autologous and allogeneic recipients. The risk of developing pneumonia did not appear to be related to the type of transplant or to the engraftment status. Two patients who did not develop pneumonia also received amantadine. The mortality rate with pneumonia was 17%. The study concluded that during community outbreaks of influenza, infection needs to be anticipated in SCT recipients. There should be serious consideration given to
prophylaxis of patients as well as their families and hospital staff, and to empiric therapy of patients with acute respiratory illness. The most appropriate drugs for prophylaxis and therapy are amantadine and zanamivir.

Other viruses
Other viruses which may cause pneumonia in the paediatric SCT setting include human herpes virus 6 (HHV6)\(^\text{16}\), varicella Zoster virus (VZV)\(^\text{37}\) and measles virus. HHV6 may act as a co-pathogen with CMV, but may also cause infective lung disease in isolation\(^\text{38}\). Re-activation of VZV (nearly always \(> 100\) days) is common in transplant recipients (\(> 50\%\)) and may occasionally be associated with pneumonia and other forms of visceral involvement\(^\text{37}\). Measles virus may be making a comeback in the community with the recent fall off in immunisation rates due to parental fears over the perceived danger of immunisation. In transplant recipients, measles may present in an atypical fashion and be associated with severe infection including pneumonitis. Early use of i.v. ribavirin may be useful in suspected cases.

Fungal infections
Aspergillus
Aspergillus spores are ubiquitous and, because of their small size, spores are commonly inhaled and reach the alveoli. Most SCT units in the UK are HEPA-filtered and are generally free of spores, but patients may be harbouring Aspergillus spores on entry to the unit. Under normal circumstances, spores are eradicated by alveolar macrophages and, if fungal hyphae are formed, neutrophils enter the lungs and destroy them. Major risk factors for invasive aspergillosis, therefore, include steroid therapy, which impairs alveolar macrophage function, and prolonged neutropenia, both of which are a frequent occurrence in patients undergoing SCT. In the absence of neutrophils, Aspergillus hyphae proliferate and invade pulmonary parenchyma, invading local blood vessels (Plate 3, see page 150) resulting in thrombosis and haemorrhagic infarction of lung tissue, and distant spread of the disease\(^\text{39}\). In previous studies, the incidence of aspergillosis was estimated at around 4\% of patients undergoing SCT, and were most commonly caused by Aspergillus fumigatus and Aspergillus flavus\(^\text{40}\). Within the GOSH patient cohort, 9/450 patients (2\%) have had proven invasive pulmonary aspergillosis (IPA) which proved to be fatal in 8/9 cases. Infection usually becomes evident in the postengraftment period and is almost always associated with prolonged neutropenia and the use of steroids to treat GvHD.

Clinical symptoms may be non-specific but the presence of pleuritic chest pain, haemoptysis and/or pleural rub should raise the suspicion. There may be evidence of disseminated infection including meningitis,
sinusitis or a space occupying cerebral lesion. Chest X-ray typically shows solitary or multiple pulmonary nodules or mass-like infiltrates (mycotic lung sequestrum), and cavitation which is frequently present in the adult population may also be seen in the paediatric population although less frequently. CT often reveals frank disease not evident on chest X-ray and may demonstrate the presence of a rim of ground glass attenuation surrounding a parenchymal nodule (halo sign), or cavitation not seen on X-ray (Fig. 5A–C). The definitive diagnosis of IPA can only be made when histological specimens show characteristic hyphae involving lung tissue. *Aspergillus* is present in less than half of sputum cultures, although culture and staining of BAL fluid may offer a significantly higher yield. Consequently, appropriate therapy should begin with the presence of a strong clinical suspicion of IPA as all cultures including percutaneous needle biopsy may be negative for *Aspergillus*. The use of *Aspergillus* PCR

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**Fig. 5** (A) Chest X-ray showing nodular consolidation in the left lower zone with corresponding CT (B,C) performed two days later, which reveals a cavitating necrotising pneumonias in the left lower lobe due to invasive pulmonary aspergillosis (IPA). The CT images show both lung parenchymal and soft tissue windows which provide better anatomical detail of the lesion.
and galactomannan assays in predicting the presence of early *Aspergillus* infection are presently under investigation.

In terms of treatment for IPA, the best current approach includes high-dose liposomal amphotericin (e.g. ambisome 5–10 mg/kg/day), usually given in conjunction with GM-CSF ± itraconazole/voriconazole. In the presence of localised lesions and for increasing haemoptysis, surgical resection with lobectomy or even pneumonectomy has been attempted. However, once established, the prognosis for IPA remains dismal as illustrated in the GOSH cohort with 8/9 patients succumbing to infection. Consequently, prevention rather than therapy of IPA must be the goal. Within paediatric practice in the UK, there is a consensus approach which includes the use of oral itraconazole solution 5 mg/kg/day from 2 weeks prior to SCT until neutrophil recovery is well established. During the SCT procedure, the presence of a fever unresponsive to 96 h of broad spectrum antibiotics should be treated empirically with ambisome 1–3 mg/kg. If *Aspergillus* PCR proves to be a reliable marker, then this may allow the earlier institution of higher doses of liposomal amphotericin in patients with early infection.

**Candida**

Although *Candida* is a common pathogen in the immediate post-transplant period and invasive infection either fungaemia or visceral organ involvement occurs in 11–16% of patients, candidal pneumonia is rare, occurring in only 1% of patients. *Candidal pneumonia* may result from haemotogenous dissemination or from aspiration from the oral pharynx. Most SCT patients would routinely receive fungal prophylaxis with itraconazole/fluconazole and therapy for breakthrough candidaemia is usually with ambisome 3–5 mg/kg ± flucytosine in refractory patients.

**Other fungi**

*Trichosporon fusarium* and *Zygomycetes* organisms are occasionally seen in patients undergoing SCT. As with other fungal infections, major risk factors include prolonged neutropenia and steroid therapy.

**Protozoal**

*Pneumocystis carinii (PCP)*

Due to routine use of prophylactic therapy, PCP is now uncommon in patients undergoing SCT and most studies report an incidence of less than 1%. Routine prophylaxis with trimethoprim/sulphamethoxazole usually starts at the time of engraftment and continues for 3–6 months post-transplant. If PCP occurs it does so mainly in the postengraftment period and has a median time to onset of 2 months. Clinicians should be particularly suspicious of PCP if for any reason a child has not been complying
with PCP prophylaxis. Clinical manifestations include non-productive cough, rapid progressive dyspnoea and hypoxia, often resulting in respiratory failure. Chest X-ray and CT typically show diffuse interstitial infiltrates in alveoli. CT may demonstrate areas of ground-glass attenuation and multiple small nodules. Diagnosis of PCP is made by visualising the organism usually in BAL fluid (sensitivity > 90%); occasionally sputum may be positive for PCP, although not as frequently as in patients with AIDS due to a much lower burden of organisms. The treatment of choice in PCP is high dose septrin. In patients with more severe PCP, most clinicians use steroids to reduce the risk of respiratory failure and death, although data in support of this were generated in AIDS patients and studies in other immunocompromised patients have not been performed. Occasionally, the combination of PCP infection and preceding high dose chemotherapy can result in lung fibrosis (Fig. 6).

**Mycobacterial infections**

Pneumonia caused by *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Mycobacterium kansasii*, and *Mycobacterium haemophilum* have been reported in patients undergoing SCT. These infections are very uncommon, and mostly reported in patients receiving immunosuppressive therapy for chronic GvHD usually more than 6 months after transplantation. 

Fig. 6 High resolution CT through the midzones of the lungs showing bilateral interstitial pulmonary fibrosis with tiny loculated pneumothorax on the left side and marked thickening of the oblique fissures bilaterally. This was related to pulmonary fibrosis secondary to a continuation of chemotherapy (busulphan) and PCP pneumonia.
Post-transplantation lymphoproliferative disease (PTLD)

PTLD is a life-threatening complication of SCT as well as solid organ transplantation. The highest incidences have been reported in heart, lung and heart-lung transplant recipients. For SCT recipients, the incidence varies from 0.6% to as high as 24% in recipients of mismatched T-cell depleted allografts. PTLD is of B-cell origin and is associated with EBV infection. In SCT recipients, PTLD usually arises in donor B lymphocytes, although occasionally it may arise in recipient lymphocytes, and is becoming increasingly recognised in recipient lymphocytes following reduced intensity conditioned transplants. Serology is not a useful tool in the diagnosis of PTLD in SCT recipients; however, viral load measurements by PCR is proving a promising tool for early diagnosis and serial monitoring. T-cell depletion of the graft is one of the most important risk factors for this disease, in particular when using methods which are relatively sparing of B-cell numbers, such as high dose anti-thymocyte globulin and anti-T-cell monoclonal antibodies. Thus, the risk of PTLD in SCT reflects the relative preservation of EBV infected B-cells and the removal of EBV-specific cytotoxic T-cell precursors. The greatest risk period following SCT is during the period of time when this imbalance is greatest, usually in the first 6 months of the SCT procedure. When PTLD affects the lungs it may appear as focal or diffuse infiltrates (Fig. 7A–C) associated with hypoxaemia and often preceded by a prolonged period of high unremitting fever often in the presence of adenopathy and hepatosplenomegaly – 5/450 (1%) of GOSH SCT patients experienced PTLD affecting the lungs; 3/5 cases followed reduced intensity conditioning in combination with ATG. All cases proved to be fatal. A variety of approaches to treatment have been explored. Withdrawal of immunosuppression and use of antiviral agents such as acyclovir or ganciclovir appear to have little effect in the SCT setting. However the use of anti-B-cell monoclonal antibodies, e.g. Rituximab, donor lymphocyte infusions, and most recently EBV-specific cytotoxic T-cells can be dramatically effective.

Idiopathic pneumonia syndrome (IPS)

IPS is used to define acute lung injury post-SCT for which no infectious agent can be found. It typically occurs around 50 days and before 100 days post-SCT. Chest X-ray and CT typically show diffuse airspace and/or intestinal infiltrates. The aetiology is thought to be multifactorial including chemoradiotherapeutic insults and GvHD. Because the lung is typically not a target organ in acute GvHD, another inciting factor is believed to be important for the development of lung injury. Some studies suggest that this factor may be a latent viral infection, e.g. CMV or HHV6. Further studies are awaited.
Diagnosis

It is important to remember that respiratory complications tend to occur after SCT in a rather well-defined temporal sequence (see Fig. 1). Certain aspects of the medical history, examination of the child, and details of the microbiological monitoring up to the onset of symptoms, are also important. The presence of rhinitis, sinusitis or otitis media

Key points for clinical practice

Fig. 7 (A) Portable supine chest X-ray showing marked overinflation of the right lung with perihilar nodular shadowing and small areas of reticular nodular shadowing, most noticeable at the right costophrenic angle. Subsequent biopsy showed this to be related to lymphocytic interstitial pneumonitis (LIP) secondary to Epstein-Barr virus. Subsequent chest X-ray (B) shows conglomerate perihilar opacification related to complicating adult type respiratory distress syndrome (ARDS). (C) High resolution CT through the upper lobes showing patchy consolidation in the posterior segments with pleural shadowing on the right. There are also dilated secondary pulmonary lobules and some minimal interstitial change. Post mortem showed these changes to be due to infiltration with polyclonal lymphocytes and plasma cells due to Epstein-Barr related lymphoproliferative disease (EBV related LPD).
would point to RSV or parainfluenza infections and those viruses should be sought from NPA. The finding of significant haemoptysis might suggest *Aspergillus* infection or non-infective causes including pulmonary embolism and diffuse alveolar haemorrhage. Children with a preceding history of severe mucositis following the preparative regimen may be more at risk of an anaerobic or candidal pneumonia. The presence of herpetic lesions on the lip or herpetic stomatitis raise the possibility of HSV pneumonia. The presence of pain localised to the chest may suggest *Aspergillus* or pulmonary embolism. Examination may reveal a pleural friction rub which would again suggest *Aspergillus* or pulmonary embolism. The presence of basal crepitations, in keeping with other features of fluid overload, might suggest pulmonary oedema. During the SCT procedure, prophylactic medications are usually given for fungal infections with itraconazole, fluconazole or ambisome, HSV and CMV using acyclovir, CMV using ganciclovir, and PCP with septrin. If any of these prophylactic measures are omitted or not tolerated, then the possibility of the corresponding infectious agent causing respiratory infection may be increased.

A chest radiograph and, in selected patients, CT of the chest, may provide additional diagnostic information (see Table 3). CT appears to be of greatest

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<th>Radiological signs</th>
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<td>Diffuse airspace and/or interstitial infiltrates</td>
<td>Idiopathic pneumonia syndrome</td>
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<td>Diffuse alveolar haemorrhage</td>
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<td>Pulmonary oedema</td>
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<td>Viral pneumonia</td>
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<td>Septic emboli</td>
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<td>Pleural-based consolidation</td>
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<td>Mycobacterial infection</td>
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<td>Relapsed malignancy</td>
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benefit in patients whose chest radiographs are either normal or show focal infiltrates. CT is less likely to provide useful information in patients with diffuse interstitial or alveolar infiltrates. The use of CT may demonstrate unsuspected interstitial alveolar infiltrates, nodules, peripheral wedge shaped infiltrates, cavitation, air crescents, halos, and lymphadenopathy. One of the problems of CT is the requirement to break the HEPA-filtered environment for the child, and secondly frequent requirement for sedation/general anaesthesia may worsen respiratory function. The requirement for sedation/general anaesthetic may be reduced by the use of modern scanners employing spiral or multislice techniques.

Positive serology prior to SCT in either the recipient or donor for both CMV and EBV place the patients at potential risk of major complications from both these viruses. However, positive serological investigations are useless following SCT as the child is unable to mount an antibody response, but PCR techniques looking for antigen is useful for CMV, adenovirus, EBV, and are under investigation for fungi. A rising viral load is particularly suggestive that a specific virus may be causative for respiratory infection. NPA may be useful for detecting RSV and parainfluenza. Samples may be obtained from the lower respiratory tract using several diagnostic techniques. By far the most common in the paediatric population is broncho-alveolar lavage. This may be performed by wedging a fibre-optic bronchoscope in the subsequent bronchus leading to an area of radiological abnormality. Aliquots of sterile saline are instilled through the bronchoscope and then aspirated into a sterile container. If the child has an enterotracheal tube in situ then blind lavage may be made by distilling fluid through a nasogastric tube placed alternatively in each main bronchus and aspirating as before. The aspirated fluid is cultured for fungi, bacteria, mycobacteria, Legionella and viruses, and examined for Legionella spp. using the direct fluorescent antibody technique. Cytospins are made of the lavage fluid and cells stained using the direct Wright-Giemsa, Papanicolaou, methenamine silver, Ziehl Neelsen, Prussian blue, to detect viral inclusions, fungi, PCP, mycobacteria and haemosiderm. In addition, fluorescein-labelled monoclonal antibodies are used to detect the presence of CMV, RSV, adenovirus, influenza and parainfluenza within infected cells. More recently, PCR techniques are used to detect CMV, adenovirus, EBV and mycobacteria. The overall sensitivity of BAL is somewhere between 30–60%. Additional techniques involving transbronchial lung biopsy and protected specimen brushing, which are performed through a fibre-optic bronchoscope, are less commonly performed in the paediatric population. In practice, if all investigations including BAL are negative, and a definitive diagnosis still required, then the usual policy is to proceed to open lung biopsy, usually performed through a limited thoracotomy incision. This is probably the gold standard method for diagnosing pulmonary disease in the immunocompromised...
patient, and several studies have reported specific diagnoses made in approximately 70% of cases. However, it is commonly complicated by a persistent air leak and delayed pneumothoraces and, although it may enable a specific diagnosis to be made and therapy to be altered accordingly, it is unknown whether open lung biopsy at this stage improves survival. An alternative to open lung biopsy is the use of videothorascopic surgery (VATS), which may achieve the same diagnostic yield with decreased postoperative morbidity; however, it does require a period of single lung ventilation and, therefore, cannot be performed in children with severe impaired gas exchange, which is common in children with diffuse pulmonary infiltrates post-SCT. There is still very little experience in the use of VATS in the post-SCT setting.

**Management**

An algorithm outlining the key points for clinical management of respiratory disease post SCT is outlined in Figure 8. Initial evaluation needs to determine whether the child can remain in the transplant unit monitored
with a transcutaneous oxygen probe, intermittent blood gases, and supported with additional oxygen, or requires transfer to the paediatric intensive care unit (PICU) for ventilatory support. Once stabilised, specific therapy should commence if the causative organism is known/suspected or, if not, empiric therapy commenced. Empiric therapy usually includes broad spectrum antibiotics, liposomal amphotericin (particularly if focal consolidation), azithromycin (for atypical pneumonia), high dose septrin, plus or minus ganciclovir depending on the perceived risk for CMV. If there are diffuse infiltrates and pulmonary oedema may be suspected, then a trial of diuretics is frequently given. Given the additional information that can be ascertained from PCR studies on blood to exclude potential causes including CMV, adenovirus, and EBV, many physicians do not at this stage move immediately to BAL as this will most certainly require a general anaesthetic, increase the respiratory compromise and necessitate ventilatory support. Empiric therapy should be commenced with additional therapy guided by PCR and NPA, and the child observed for improvement or otherwise. However, a significant number of cases do require transfer to PICU for progressive respiratory insufficiency. Support may be given in the form of constant positive airways pressure or in the more severe cases by ventilation via conventional or oscillatory means. If ventilation is required, a BAL should be performed at this point. If the BAL is diagnostic, then therapy is altered appropriately; if not, then empiric therapy is continued.

Several studies have suggested that in the SCT setting unless improvement in respiratory compromise is seen within 72 h, then eventual survival is extremely unlikely. It may be reasonable at this point to withdraw further support as additional treatment is futile. The prognosis for paediatric SCT patients requiring admission to PICU for ventilatory support in a subset of 210 GOSH patients over a 5-year period was studied from 1994–1998: 31 (14.8%) required intubation with mechanical ventilation during 36 admissions and although 15 of these episodes (41.6%) resulted in patients being discharged from PICU only 4 patients (12.9%) were alive 6 months post-SCT. Consequently, in the setting of paediatric SCT, every effort should be made to prevent, or aggressively manage, respiratory complications early, so as to reduce the need for mechanical ventilation from which point few children recover.

References

Respiratory infections following paediatric SCT

Childhood respiratory diseases


