PAEDIATRIC RESPIRATORY REVIEWS (2007) **8**, 46–61

Paediatric Respiratory Reviews

REVIEW

Pulmonary complications of haematopoietic cell transplantation in children

Peter H. Michelson*, Rakesh Goyal and Geoffrey Kurland

Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA

KEYWORDS
bone marrow transplantation;
bronchiolitis obliterans;
children;
complications;
cytomegalovirus;
obliterative bronchiolitis;
pneumonia;
stem cell transplantation

Summary Paediatric haematopoietic cell transplantation has experienced significant advances in the last few decades. However, pulmonary complications are an important limitation to the efficacy of this intervention, contributing to post-transplantation morbidity and mortality. Such complications persist even in experienced centres and occur in adult and paediatric recipients. This review identifies the paediatric pulmonary complications that are commonly seen following haematopoietic cell transplantation and addresses both infectious and non-infectious aetiologies and their clinical manifestations, evaluation, and potential therapy. Ultimately, improvement in outcomes will require attention to immunosuppression as well as traditional diagnostic procedures and treatment. This article aims to review the current state of pulmonary complications post-transplantation, to examine the impact of our recent advances and changes in treatment, and to identify potential future therapies and hypothesise what role these might have on long-term survival.

INTRODUCTION

The first clinical interventions involving the use of bone marrow date back to the 1890s, when anaemia associated with leukaemia was treated with the oral administration of bone marrow.[1] In 1923, saline extracts of bone marrow and spleen were administered – either orally or intravenously – to treat certain secondary anaemias. In the following decade, intramuscular injections of freshly prepared autologous or allogeneic bone marrow for patients with anaemia secondary to malaria or helminthic infections were reported.[2] The first detailed description of the intramedullary injection of bone marrow to treat aplastic anaemia was reported in 1940.[3]

Subsequent advances in transplantation biology and immunology, combined with innovations in chemotherapy and irradiation, have allowed haematopoietic cell transplantation to become a more viable therapeutic intervention in the treatment of haematologic diseases. The science of bone marrow transplantation, which began as the allogeneic transplantation of whole bone marrow, has progressed to include allogeneic altered marrow (e.g. T-cell depleted), autologous marrow and stem cell transplantation. Despite many advances in this field, even the most experienced centres encounter significant post-transplantation morbidity and mortality. Infectious and non-infectious pulmonary complications remain common following marrow transplantation both in adults[4–6] and children.[7–9]

It should also be noted that most of the studies of the recipients of haematopoietic cell transplantation deal with adults rather than children, but many important principles apply across age barriers. Although different sources for transplantation (e.g. allogeneic or autologous)

* Corresponding author. Division of Pediatric Pulmonology, Children's Hospital, of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, PA 15213, USA. Tel.: +1 412 692 5630; Fax: +1 412 692 6645.
E-mail address: peter.michelson@chp.edu (P.H. Michelson).

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doi:10.1016/j.prrv.2006.04.003

have different incidences of particular complications, we will describe potential complications in a more general fashion and will refer to relative incidences when appropriate.

The most recently available data from the International Bone Marrow Transplantation Registry show that the overall number of transplants continues to increase. In addition, the number of autologous transplants performed now exceeds the number of allogeneic transplants, and the rate for the former is increasing faster than that for the latter. However, although autologous transplantation greatly decreases the risk of graft-versus-host disease (GVHD) and the need for increased immunosuppression, autologous transplants are by no means free of complications.

We have chosen to refer to these procedures collectively as haematopoietic cell transplantation (HCT), although other texts or review articles have used the term 'stem cell transplantation'. This article speaks to the broad range of pulmonary complications of HCT in paediatric recipients. Although these complications vary in incidence depending on the type of transplant, the persistence of these problems across all procedures is well documented. Those conditions that are more common will be given more attention, although the authors acknowledge that each of these entities carries the possibility of serious morbidity and, in too many cases, mortality for those recipients who develop them.

We have organised this article in a way that will facilitate the differentiation of common complications. First, we discuss the important factors that can predispose recipients to pulmonary complications following HCT. Second, we outline the non-infectious complications of HCT most commonly seen during the early phase (<100 days) after transplant. As infectious complications occur throughout the post-transplantation period, we complete a discussion of infectious complications of HCT before returning to discuss those non-infectious complications encountered later in the post-transplant course. Throughout the article, we intersperse potential diagnostic and therapeutic options for many of these complications, their risks and potential benefits, and their overall impact on survival. Finally, we outline areas we consider ripe for future research in the area of pulmonary complications of pediatric HCT.

PRETRANSPLANT FACTORS

Some pre-existing diseases that themselves necessitate HCT can have pulmonary complications that will impact post-transplantation pulmonary health. An example of this circumstance is sickle-cell disease (SCD). SCD is often complicated by acute chest syndrome, which can lead to pulmonary infarction or other lung injury.[10] More recently, pulmonary hypertension has been recognized as an important complication of SCD, with additional associated morbidity.[11] Both of these complications are likely to have a negative effect on pulmonary function following HCT.

Patients with underlying malignancies resulting in the need for HCT treatment might have been treated with cytoreductive agents or irradiation targeting the lung. Several chemotherapeutics, including bleomycin, busulfan, and cyclophosphamide are known pulmonary toxins, leading to a range of pulmonary complications including fibrosis and pneumonia.[12] Several of these agents are also used to condition patients in preparation for HCT and are associated with pulmonary toxicity including interstitial fibrosis. Although the mechanism(s) involved are unclear, the target appears to be the vascular endothelium. With bleomycin, primary endothelial damage leads to fibroblastic metaplasia and interstitial lung disease.[13] Lung irradiation, either as treatment of a primary malignancy, pulmonary metastatic disease, or as part of a conditioning regimen in preparation for HCT, can also result in pulmonary disease, manifest mainly as either pneumonitis or pulmonary fibrosis.[14] As will be discussed below, it is crucial that patients previously exposed to agents that are potentially 'pneumotoxic' have pre-HCT pulmonary screening. As might be expected, the impact of conditioning regimens on post-HCT complications has led to alterations in the intensity of these regimens. A recent report demonstrates that this approach might lead to improved survival with diminished toxicity in selected circumstances, such as in recipients with primary immunodeficiency who are to receive HCT from an unrelated human lymphocyte antigen (HLA)-matched donor.[15]

A variety of other pre-HCT factors might adversely affect post-HCT pulmonary status and complications. These include pulmonary infections, thoracic surgical procedures, viral illnesses and chronic aspiration and/or gastroesophageal reflux. Severe lower respiratory infections, particularly invasive fungal disease, can increase the risk of both recurrent infection and pulmonary debilitation post-HCT. The increased risk of recurrent fungal infection in patients undergoing intensive chemotherapy similar to that required for HCT conditioning[16] led to more widespread use of anti-fungal prophylaxis, especially in patients at risk for recurrence following HCT.[17] Although the possibility of recurrent fungal disease post-HCT is concerning, it is now felt that adequate pre- and post-transplant treatment of fungal disease, either with anti-fungal antibiotics, surgical resection of isolated foci of infections, or both, now allow HCT to be considered in such patients.[18,19]

Thoracic surgical procedures used in the treatment of primary disease are common before HCT. These can include lobectomy or wedge resection of nodules involved with pulmonary metastatic disease or associated with the diagnosis of localized fungal infections. The risk of HCT closely following thoracic surgery is probably increased, but this will depend on the type of surgical approach taken, the amount of lung tissue removed, the patient's underlying nutritional status, and other factors such as neutropaenia. When performed via thoracotomy, such procedures also

carry the risk of postoperative pain and splinting, which can lead to decreased cough and resultant atelectasis. In addition, chest tube placement is common following open thoracotomy, and this can prolong the postoperative recovery, although tube thoracostomy is not an absolute contraindication to HCT.[20] Minimally invasive thoracoscopic surgery can be used for these procedures in children as well as in adults,[21] which can result in decreases in postoperative pain and morbidity. Furthermore, it often can be completed without requiring prolonged presence of a chest tube, speeding the return of the patient to optimal pulmonary status.[22]

Cytoreductive therapy and irradiation alter host defences and disturb mucosal integrity. These untoward effects can lead to the colonisation with pathogens that might become problematic in the post-HCT period. Chronic oesophagitis has been recognised as a risk factor for patients with underlying malignancies. Potential HCT recipients with dysphagia or odynophagia should be evaluated for oesophagitis, as the damaged oesophageal mucosa, aided by neutropaenia, increases the risk of oesophageal colonisation with organisms including *Candida* spp. and herpes simplex. The role of oesophagoscopy to help direct therapy for such patients has been documented previously.[23] In addition, gastroparesis and delayed gastric emptying resulting in nausea, gastrooesophageal reflux or decreased oral intake might be seen following HCT.[24,25]

Finally, malnutrition is common in paediatric patients being considered for HCT. A recent study suggests that the measured body cell mass adjusted for height (BCM/Ht) is more accurate than the body mass index (BMI; weight in kilograms divided by the square of height in metres) at determining the degree of malnutrition in these patients.[26] Because myeloablative and irradiative conditioning regimens can lead to mucositis, which will decrease oral intake, and because malnutrition is felt to be an independent risk factor for mortality following HCT,[27] enteral or parenteral feeding is common following HCT.[28,29] Newer strategies have been developed to decrease regimen-related toxicity (such as mucositis) by a combination of vitamins, ursodeoxycholic acid, and parenteral nutrition titrated to equal the energy expenditure of the patient; although studies are limited, they suggest that nutritional support might have a role beyond mere prevention of malnutrition and could be useful to promote earlier engraftment and a decrease in toxicity.[30]

RESPIRATORY ASSESSMENT PRE-HAEMATOPOIETIC CELL TRANSPLANTATION

Pulmonary complications following HCT are relatively common and carry significant morbidity and mortality. As noted above, pulmonary dysfunction and the presence of other risk factors, such as gastrooesophageal reflux, can negatively impact the respiratory system following HCT. For these reasons, it is recommended that a thorough history and review of systems be obtained, and a clinical assessment of the patient's pulmonary status be completed before HCT, as outlined below:

- History/physical examination
- Laboratory studies:
  - renal (24-h creatinine clearance)
  - hepatic
  - immunoglobulins
  - haematologic
  - nutritional: albumin, total protein, vitamin levels
  - serologies: human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), hepatitis
- Chest X-ray
- Electrocardiogram (EKG) and echocardiogram
- Chest CT scan (thin cut, high resolution)
- Pulmonary function testing (this will depend on patient age and cooperativity):
  - spirometry
  - lung volumes
  - transfer factor (diffusing capacity)
  - maximal inspiratory/expiratory pressure
- 6-minute walk test
- Nutritional consultation.

Pulmonary function testing, including the determination of lung volumes and diffusing capacity, provides useful baseline measurements. Such testing documents the presence of lung disease, which might represent a primary manifestation of the underlying illness (e.g. neoplasm with pulmonary metastatic disease), complications of the underlying illness (e.g. pulmonary infarction secondary to sickle-cell anemia), or other pre-existing pulmonary conditions (e.g. asthma).[31]

Musculoskeletal weakness is a known complication of HCT and is common even before HCT is carried out.[32] The recent findings of White and co-workers suggest that pre-HCT testing often reveals the presence of this problem prior to HCT and several testing modalities (6-minute walk test and respiratory muscle strength testing) are useful in identifying patients at risk.[33] The determination of respiratory muscle weakness prior to HCT can allow for more concerted efforts toward musculoskeletal rehabilitation and nutritional support in both the pre- and post-HCT periods.

Chest radiographs or, in selected cases, CT scans, should be obtained before initiating ablative chemotherapy and HCT. These studies will be useful as baseline studies should there be post-HCT pulmonary complications such as pulmonary oedema, pulmonary haemorrhage, pneumonia, or bronchiolitis obliterans (BO).[34]

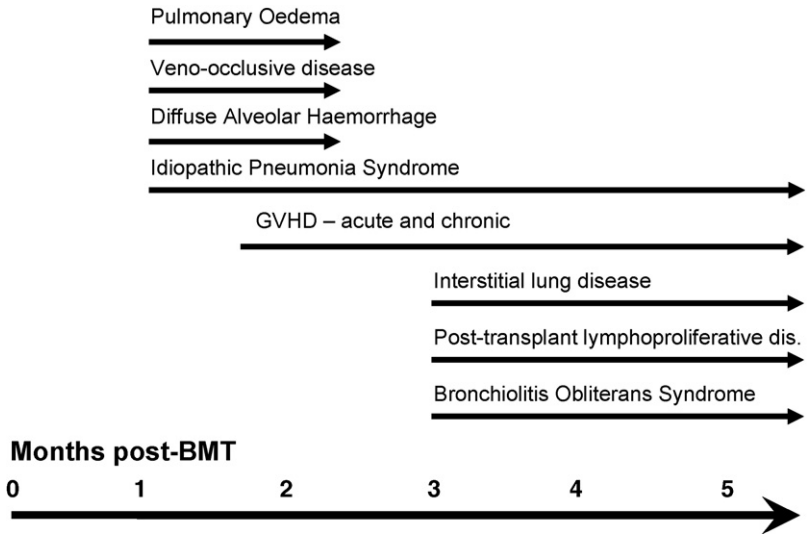

Figure 1 Timeline of non-infectious pulmonary complications.

EARLY NON-INFECTIOUS POST-TRANSPLANT COMPLICATIONS (FIG. 1)

Oral and peri-oral complications

Oral mucositis has long been recognised as a significant complication following HCT. It remains common, affecting the majority of patients undergoing HCT[35] and can lead to dysphagia as well as to laryngeal or epiglottic oedema resulting in upper airway obstruction.[36] It is recognized to increase the risk of infection, lengthen hospital stay, and increase the cost of care.[37] Although oral mucositis is thought to represent the deleterious result of the combination of intensive chemotherapy and irradiation,[38] other important factors such as bacterial colonisation of the mucosal surface, upregulation of proinflammatory cytokines, and oxidative radical production play an important role.[35,39,40] It is usually seen within the first week of irradiation, and reaches its peak 1–2 weeks following HCT.[41] The complicating feature of impaired mucociliary clearance in the nasopharynx is a common co-morbidity. Together, these changes can result in both upper and lower airway symptomatology, including sinusitis, oropharyngeal bleeding, upper airway obstruction, stridor, and aspiration pneumonia. Advances in the understanding of the pathophysiology of oral mucositis have led to newer treatments including dietary manipulation, mucosal administration of monochromatic light, and the administration of cytokines such as keratinocyte growth factor.[30,35,42]

Pulmonary oedema

Pulmonary oedema in the post-transplant period is relatively common.[9,43,44] It generally is characterized by a rapid onset and usually occurs within the 2–3 weeks following transplantation. Potential aetiologies include increased hydrostatic pressure from either over-vigorous rehydration or fluid overload via parenteral nutrition, cardiac dysfunction following the use of anthracyclines, and renal toxicity following cyclophosphamide. Other causes of increased pulmonary capillary permeability include sepsis, pulmonary irradiation, and pulmonary toxicity secondary to chemotherapy. Clinical features might include dyspnoea, tachypnoea, weight gain, hypoxaemia, and basilar crackles on chest auscultation. Chest radiographs often show bilateral infiltrates and pleural effusions might also be present. If suspected, vigorous diuresis is indicated and should be initiated prior to more invasive studies such as bronchoscopy and bronchoalvoelar lavage (BAL).

Peri-engraftment respiratory distress syndrome

This entity has a low incidence (~5%) and occurs within the first 14 days following HCT, at a time coinciding with neutrophil engraftment.[45–47] The characteristic clinical and radiographic features include hypoxia and respiratory distress. Chest radiographic findings include diffuse edema and pulmonary infiltrates and in some cases pleural effusion.[48] BAL and other invasive studies are consistently negative for pathogens. Although its name and timing might suggest a specific pathology, there are no biochemical markers or pathognomonic histopathologic findings to distinguish it from other forms of respiratory distress in the period closely following HCT. Therapy is supportive, and although steroids have been often utilised for treatment, their efficacy is unproven.

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS), also known as idiopathic interstitial pneumonitis, has a reported incidence of

5–10% in adult HCT recipients,[49,50] although the incidence in paediatric recipients is more difficult to assess. A National Heart, Lung, and Blood Institute Workshop, published in 1993,[51] refined the definition of IPS and established clinical and diagnostic criteria for it. Accordingly, the clinical manifestations of IPS include dyspnoea, non-productive cough, hypoxaemia, and crackles on auscultation; pulmonary function testing reveal a restrictive pulmonary physiology and diffuse or non-lobar infiltrates are seen on chest radiograph. To qualify as IPS, BAL must be negative for bacterial, viral, and fungal pathogens; a second negative BAL is recommended[2–14] days after the initial BAL. Open lung biopsy is not specifically suggested, although transbronchial biopsy might be considered if the patient's condition will allow it. Pathologically, IPS can have two distinct histopathologic types: interstitial pneumonia and diffuse alveolar damage. IPS is typically an early complication of HCT. Previous reports of IPS incidence described a bimodal pattern, with an initial peak approximately 2 weeks and a later peak 6–7 weeks post-HCT.[51] An entity essentially identical to IPS can be seen >100 days following HCT; the incidence of this much later complication is unknown.[51]

Of special interest is a review of >1000 HCT recipients,[50] in whom the overall incidence of IPS was 7.3%, with no significant difference in incidence between recipients of autologous and allogeneic HCT. Paediatric patients (<20 years of age) had a slightly lower incidence of IPS. The median time between HCT and onset of symptoms of IPS was 21 days; the hospital mortality was 74% and multi-organ failure rather than isolated respiratory failure was associated with mortality. Possible causes include direct pulmonary toxicity resulting from pre-HCT conditioning, as well as immunologically mediated factors resulting from alloreactivity.[52–55] Treatment for IPS remains supportive; steroids, although often used, have not been shown to have a beneficial effect. The need for mechanical ventilation in these patients is associated with a poor prognosis and most patients requiring this degree of support do not survive.

Diffuse alveolar haemorrhage

Although pulmonary haemorrhage diagnosed by BAL was first reported in immunocompromised patients by Drew and co-workers,[56] Robbins *et al.* are generally credited with the description of what is known as diffuse alveolar hemorrhage (DAH) in recipients of HCT.[57] This entity appears to be much more common in adult than in pediatric recipients of HCT.[57,58] It usually appears within 30 days post-HCT and coincides with marrow recovery. Of interest is the finding of relative BAL neutrophilia, despite peripheral leucopaenia.[57] A recent retrospective analysis of paediatric HCT recipients suggests that the incidence of DAH is approximately 5%, with allogeneic recipients being especially at risk.[59] The clinical onset is often relatively sudden and rapidly progressive, with dyspnoea, hypoxaemia, and crackles on auscultation. On BAL, the characteristic feature is that with each successive aliquot instilled, the effluent becomes more haemorrhagic.[57] However, the specificity and sensitivity of the findings are not completely clear. Agusti and co-workers reported on 4 of 8 HCT recipients who had DAH on post-mortem and non-haemorrhagic BALs, whereas 7 of 13 patients without pathologically proven DAH had hemorrhagic BALs.[60] Thus, clinical correlation, timely performance of BAL, and sampling of multiple sites might be important in establishing the presence or absence of DAH.

Once diagnosed, DAH is associated with high mortality in adults (estimated at ~80%), although a retrospective study by Metcalf and associates suggests that high-dose corticosteroids might have some effectiveness as a treatment.[58] A retrospective study of paediatric patients reported that the short-term survival in this population might be somewhat higher but that relapse, with high mortality, is common.[59]

Pulmonary and hepatic veno-occlcusive disease

First reported by Troussard and co-workers, pulmonary and hepatic veno-occlcusive disease (VOD) presents as a form of pulmonary hypertension, with dyspnea, signs of right-sided heart failure, and pulmonary infiltrates on chest radiographs.[61] Children comprise the most significant proportion of HCT recipients affected by VOD.[62,63] Hepatic VOD, another vascular complication of HCT, is often associated with pulmonary VOD and interstitial pneumonitis.[64] In both, small veins and venules are partially or completely occluded by intimal fibrosis. The explanation of the relatively common coexistence of hepatic and pulmonary VOD is unknown. Possibilities include coexistent underlying toxicities or genetic factors.[65]

The diagnosis of pulmonary VOD requires a high index of clinical suspicion, as many cases reported in the literature are diagnosed post-mortem.[63] Echocardiography, cardiac catheterisation, BAL to rule out intercurrent infection, and transbronchial or transthoracic lung biopsy are potential clinical investigations that should be tailored to the patient's condition and to the clinical circumstances. Treatment options for pulmonary VOD are few, although recent reports demonstrate that defibrotide, a polydeoxyribonucleic acid with fibrinolytic and anti-thrombotic properties, might be effective therapy for hepatic VOD.[65,66] Studies of this drug in the treatment of pulmonary VOD are not complete but might prove to be useful.

INFECTIOUS POST-TRANSPLANT COMPLICATIONS (FIG. 2)

Phases of immune recovery

The recovery of immune system following myeloablative conditioning and HCT can be divided into three phases:

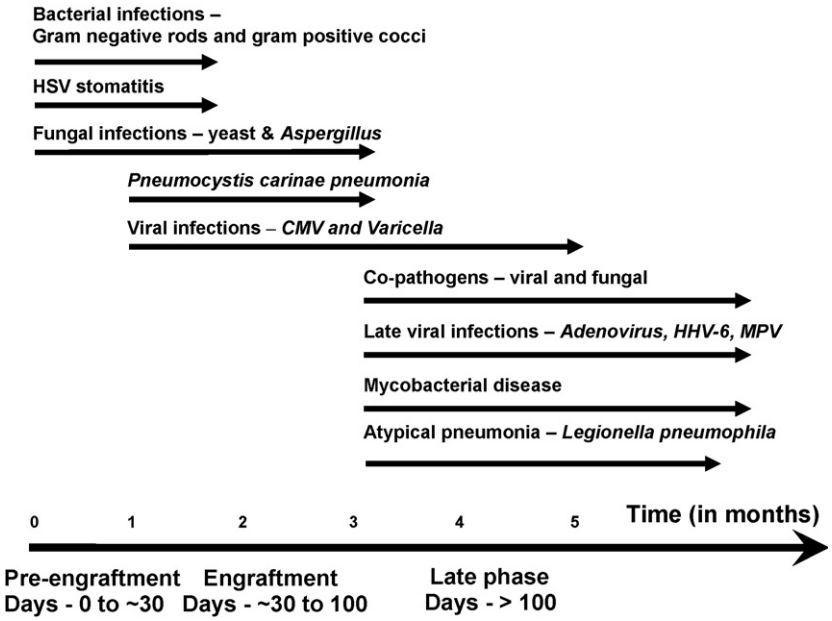

Figure 2 Timeline of infectious pulmonary complications.

The pre-engraftment phase, from day 0 to day 30 or less, encompasses the time of neutrophil count recovery; the post-engraftment phase is considered as day 30 to day 100 after HCT, and the late phase follows day 100. Each phase is characterised by a susceptibility to certain types of infections correlating with the status of the immune system at that time point.[67]

Risk factors for infections during the pre-engraftment phase

The primary immunologic defect in the pre-engraftment phase is neutropaenia. The risk for opportunistic infections is further increased during this phase because of the breakdown of mucosal barriers resulting from transplant chemoradiotherapy and from the presence of centrally placed intravenous catheters. The increasing use of granulocyte colony stimulating factor (G-CSF)-primed peripheral blood progenitor cells instead of bone marrow, especially for autologous transplants, results in faster neutrophil engraftment and a possibly decreased risk of infections.[68] On the other hand, engraftment is relatively delayed after umbilical cord blood transplants and might be responsible for a greater risk of infections in this circumstance.[69]

Risk factors for infections during the post-engraftment phase

The dominant immunologic defect in the post-engraftment phase is impaired cell-mediated immunity. Even in the absence of GVHD, all patients experience an impairment of cell-mediated immunity after HCT; this might not recovered fully until 1 year after HCT.[70–72] The post-engraftment phase can be an especially high-risk period for infections in allogeneic HCT recipients, particularly in those patients with acute GVHD who are receiving a prolonged course of corticosteroids or in recipients of T-cell-depleted grafts who received anti-lymphocyte antibodies.[73]

Risk factors for infections during the late phase

The late phase is characterised by gradual immune reconstitution with tapering and discontinuation of immunosuppressive agents. This occurs at 6 months for most allogeneic HCT patients. However, prolonged immunodeficiency – characterised by decreased immunoglobulin levels – can occur in patients with chronic GVHD, those on immunosuppressive therapy, and the recipients of T-cell-depleted and/or mismatched grafts.[74]

Infections during the pre-engraftment phase

Bacterial infections predominate during this phase. Historically, Gram-negative organisms such as *Pseudomonas* spp. were the most common pathogens encountered during this period, often causing deep tissue infections with significant morbidity and mortality.[75] Over the last decade, however, most centres have seen a shift towards Gram-positive bacteria such as *Staphylococcus aureus* (including methicillin-resistant organisms), coagulase negative *Staphylococcus* spp., *Streptococcus viridans*, and *Enterococcus* spp.[76] This shift might be related to the routine use of indwelling, tunneled catheters in children, and to the increasing use of fluoroquinolones for anti-microbial prophylaxis in adults. These Gram-positive organisms result primarily in the development of deep tissue infections, not pneumonia, as a result of catheter-related bacteraemia leading to haematogenous dissemination.

Delayed engraftment, with extended periods of neutropenia, is associated with a greater risk of invasive fungal infection. The rate of systemic *Candida* infections is approximately 15%, most frequently presenting with fungaemia and subsequent spread to the lungs, skin, and other viscera.[77] Although prophylaxis with fluconazole, as well as the use of haematopoietic growth factors, has resulted in a reduction in the frequency of early *Candida* infections, many institutions experienced an increase in azole-resistant non-albicans *Candida* infections,[78–82] In response to this, caspofungin appears to be an excellent alternative; it has less toxicity than amphotericin B and improved coverage against systemic *Candida* infections when contrasted to fluconazole.[83]

Occasionally, *Aspergillus* spp. or other filamentous fungal infections can occur during the pre-engraftment period. This appears most commonly in children who require significant myeloablative therapy prior to HCT, such as those children with acute myeloid leukaemia or relapsed acute lymphoblastic leukaemia. Unless, the patient has a history of *Aspergillus* infection prior to HCT, the risk filamentous fungal infection is much greater in post-engraftment period. Additionally, the risk is increased if the patient experiences a longer delay in neutrophil engraftment.[75]

In more than two-thirds of patients, HSV seropositive patients develop active infection, usually in the form of ulcerative stomatitis.[84,85] HSV can also cause either localized bronchopneumonia or a diffuse interstitial pneumonitis. The former is felt to be secondary to direct spread from infected oropharyngeal secretions, whereas the latter appears to be secondary to haematogenous viral dissemination.[86] Although prophylaxis with aciclovir is currently recommended for HSV seropositive patients following HCT,[84,85,87] aciclovir might not always be protective against these respiratory complications. If there is concern regarding respiratory tract infection with HSV, *in vitro* testing for anti-viral sensitivity and the administration of alternative anti-viral treatment might be warranted when proven HSV pneumonitis occurs.[88]

Infections during the post-engraftment phase

Invasive *Aspergillus* and other fungal infections occur in approximately 15% of allogeneic HCT recipients during the post-engraftment phase (Fig. 3).[89–91] The classic presentation of pulmonary aspergillosis consists of fever, pleuritic chest pain, dyspnoea, and hemoptysis. Imaging studies reveal either nodular or cavitating infiltrates; chest CT reveals the 'halo sign'.[91] Tracheobronchial aspergillosis can present bronchoscopically as a yellowish-white to gray pseudomembrane comprised of necrotic material tightly adherent to the bronchial mucosa. Although direct tissue sampling by needle biopsy or transbronchial biopsy is recommended for diagnosis, the angioinvasive nature of *Aspergillus* increases the risk of bleeding or secondary infection following such procedures.[92] As *Aspergillus* spp. can be isolated from BAL fluid in 30–50% of cases, the use of flexible bronchoscopy/BAL in this circumstance is advocated.[91,93] Assessment for extra-pulmonary manifestations, including sinus evaluation, is also recommended as extra-pulmonary aspergillosis is often fatal in HCT recipients. *Aspergillus* galactomanan antigen detection and other blood tests currently under development offer the promise for accurate diagnosis without invasive procedures such as needle biopsy or transthoracic lung biopsy.[94]

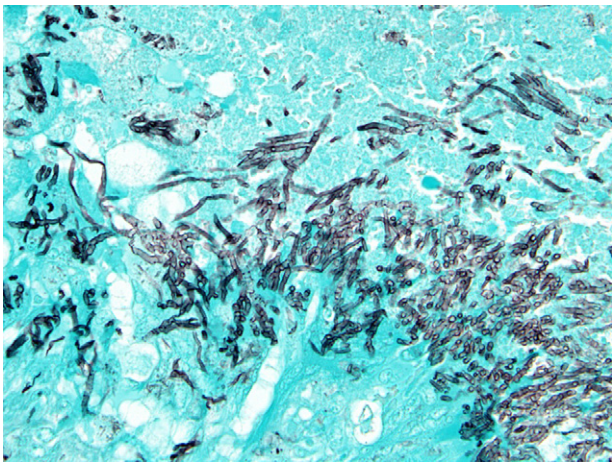

Figure 3 Invasive aspergillosis seen in a patient with pulmonary complications post-HCT. Grocott stain, 400×.

Although amphotericin B was initially the sole anti-fungal agent with activity against *Aspergillus*, newer agents are available and include voriconazole, a recently introduced broad-spectrum azole, which has excellent activity against *Aspergillus* and might become the treatment of choice for invasive aspergillosis.[83,95,96] Alternative therapies for aspergillosis include lipid formulations of amphotericin B, caspofungin or intravenous itraconazole. Agents under development include posaconazole, which has good activity against a broad range of fungal infections including mucormycosis, a fungal pathogen that is aggressive and relatively resistant to voriconazole.[97] Both posaconazole and voriconazole have activity against *Fusarium* spp. and *Scedosporium* spp., two pathogens that are notoriously difficult to treat.

'Early' CMV reactivation can occur in 50–80% of seropositive allogeneic HCT recipients during this phase.[98] Whereas CMV infections are rare following autologous transplants, graft-processing such as T-cell-depletion and/or CD34 selection in autotransplants for autoimmune diseases or neuroblastoma can be associated with increased risk.[99] Patients treated with anti-lymphocyte antibodies such as polyclonal equine or rabbit ATG, or with monoclonal antibody preparations (anti-CD25 (daclizumab or basiliximab), anti-CD3 (visilizumab), or anti-CD52 (alemtuzumab) are at high risk of CMV disease, as well as EBV-driven post-transplant lymphoproliferative disorder (PTLD) and other opportunistic pathogens.[100–102]

CMV pneumonitis presents with non-productive cough, low-grade fever, dyspnoea, and hypoxia and can be rapidly fatal without prompt therapy. To facilitate treatment, there have been significant advances in early diagnosis of CMV reactivation with shell vial culture, antigen detection, and polymerase chain reaction (PCR) assays.[103–105] Likewise, prophylactic and pre-emptive strategies using ganciclovir, foscarnet, and high-titer anti-CMV IgG have led to substantial reduction in incidence and mortality of CMV disease.[67,98] New data are emerging on the use of valganciclovir (a ganciclovir analog with increased oral bioavailability) for the prevention and treatment of CMV disease.[106]

Varicella zoster virus (VZV) reactivation following HCT might or might not present with the classic vesicular eruption; however, infection with VZV can lead to complications including visceral dissemination, pneumonia, hepatitis and encephalitis.[107] Aciclovir prophylaxis is recommended for seropositive patients with history of natural chicken pox.[67,108] Intravenous aciclovir is currently the treatment of choice for reactivation HSV disease in the HCT recipient. The relatively new pro-drug valaciclovir has excellent oral bioavailability and might be preferable in selected cases.[109]

Pneumocystis carinii (PCP) pneumonia might occur because of reactivation of latent organisms or from person-to-person transmission. Children with congenital immunodeficiency disease and patients receiving chronic immunosuppressive therapy are especially at risk. Presenting symptoms usually include dyspnoea, cough, hypoxaemia, and fever with limited findings on physical examination. Whereas some patients might have bilateral pulmonary infiltrates on chest X-ray, minimal or absent X-ray findings are reported in up to 15% HCT patients.[110] BAL is positive in most patients, making transbronchial or open lung biopsy rarely necessary.[110] Trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis (doses delivered 2–3 days per week) is recommended; myelosuppression and hypersensitivity are potential adverse effects. Alternative agents for prophylaxis include daily dapsone or atovaquone. For those recipients older than 5 years of age who have had untoward reactions to TMP/SMX or other oral agents, monthly aerosolised pentamidine, 300 mg via Respirgard II nebuliser (Marquest, Engelwood, CO, USA) is recommended.[67,111] For proven PCP infection with moderate to severe hypoxaemia, high-dose TMP-SMX with adjuvant glucocorticoid therapy remains the treatment of choice.[112]

Infections during the late phase

Late opportunistic infections are relatively uncommon after autologous transplantation, except in instances of non-adherence with aciclovir prophylaxis resulting in VZV reactivation.[113] GVHD, a more common complication in recipients of allogeneic HCT, might lead to further immune compromise with progressive hypogammaglobulinemia, poor opsonisation, and impaired reticuloendothelial function.[114–116] As a result, these patients are particularly vulnerable to severe infection by encapsulated bacteria, including *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitides*.[117,118]

'Late' CMV has been observed in those with active GVHD, on high doses of steroids (>1 mg/kg of prednisone), with low CD4 counts, with a history of prior CMV reactivation, or with extended use of anti-CMV treatment or prophylaxis.[119] Reduced-intensity conditioning regimens or so-called 'mini-transplants' with fludarabine, single-dose radiation, and post-transplant cyclosporine and mycophenolate mofetil is an emerging treatment for patients who are not candidates for standard myeloablative conditioning.[120] These patients have shorter period of neutropaenia and less risk of CMV disease and viremia during the first 100 days but might subsequently be faced with a delayed onset of CMV disease. Unlike early onset disease, which is characterised mainly by interstitial pneumonitis:[121] late CMV manifestations include retinitis, marrow failure, or encephalitis.[119,122]

Other late-phase infectious agents

Pulmonary co-pathogens

It is not unusual to find co-pathogens, i.e. isolation of more than one pathogenic species of bacteria, fungus, or opportunistic virus, in BAL or lung biopsy specimens. Pulmonary co-pathogens have been isolated in as many as 53% of patients with parainfluenza pneumonia.[123] HCT recipients with CMV disease or respiratory viral infections are more susceptible to invasive fungal infections, especially *Aspergillus*.[124] Alangaden and colleagues described occurrence of Gram-negative bacilli and *Aspergillus* infections among allogeneic bone marrow transplant (BMT) recipients with chronic GVHD on steroids.[125] In our own series of patients at this institution, we have seen a variety of microorganisms, including *Escherichia coli*, *Aspergillus fumigatus*, *Enterococcus* spp., and non-tuberculous mycobacterial (NTM) species either as pulmonary colonisers or co-pathogens. Chronic colonisation of the airways of patients with GVHD might be analogous to colonisation of the respiratory tract with *Pseudomonas* and *Aspergillus* spp. in patients with cystic fibrosis, possibly suggesting an alteration in the homeostasis of the respiratory mucosa, mucociliary clearance, and airway surface liquid. Recovery of bacteria from respiratory secretions in this scenario might represent airway colonisation rather than invasive parenchymal disease.

Adenovirus

Adenovirus, often considered endemic in the general population, might be community acquired or occur as a nosocomial infection from hospital staff. Adenoviral infection typically presents with fever, pharyngitis, cough, and conjunctivitis, with or without nonspecific pulmonary infiltrates on chest X-ray.[126,127] In addition to pneumonia in susceptible HCT recipients, adenovirus can result in hepatitis, gastroenteritis, hemorrhagic cystitis, or encephalitis. Because of the

multiple organ presentation, it can clinically resemble CMV disease, thus making the diagnosis even more difficult.[128]

Adenoviral pneumonia in an immunocompromised host can rapidly evolve into necrotising bronchitis and bronchiolitis. The diagnosis can be made on viral culture of BAL fluid or demonstration of typical viral inclusions from bronchial brushings. The possibility of adenovirus should be considered in cases of diffuse pneumonia that fail to respond to what is considered appropriate therapy, if there have been instances of acute respiratory disease in the community, or if there is associated renal or hepatic involvement. Kampmann and colleagues recently described an approach using prospective monitoring for adenoviraemia utilizing a sensitive polymerase chain reaction method, early anti-viral therapy with intravenous ribavirin, and/or cidofovir and prompt withdrawal of immunosuppression of affected paediatric HCT recipients.[129] In this study, adenoviraemia was detected in 26/155 (17%) of transplant recipients and was found exclusively in patients who had received T-cell-depleted grafts. Mortality from disseminated adenoviral infections was 5/26 (19%) in this study, which is significantly lower than previously reported.[130]

Human herpesvirus-6

Human herpesvirus-6 (HHV-6), the aetiologic agent for roseola, persists in dormant form but can frequently undergo reactivation in immunocompromised HCT recipients. Clinical associations with HHV-6 viral replication have included fever, myelosuppression, pneumonia, and other visceral involvement. However, a causal relationship with this viral infection has not been clearly established.[131]

Human metapneumovirus

Human metapneumovirus (hMPV) is a newly described viral infection that accounts for a large proportion of cases previously relegated to 'undiagnosed' respiratory infections, particularly in young children.[132,133] It has a seasonality similar to that of Respiratory Syncytial Virus (RSV), i.e. winter epidemics, with variation in severity from year to year. Martino and colleagues recently described isolation of hMPV as a pathogen (i.e. without any documented co-pathogen) in 11/177 (6.2%) of nasopharyngeal aspirates from symptomatic adult HCT recipients. An additional five patients had hMPV as a co-pathogen, one with *Aspergillus*, and one with *Aspergillus* and CMV, and three with other respiratory viruses (adenovirus, RSV, or influenza). Fifty per cent of the infections were considered nosocomial; pneumonia complicated hMPV upper respiratory tract infections in 4 (44%) of 9 and 1 (14%) of 7 allo-HCT and auto-HCT recipients, respectively.[134]

Mycobacterial infections

The development of disseminated *Mycobacterium tuberculosis* following HCT is a serious and often fatal complication

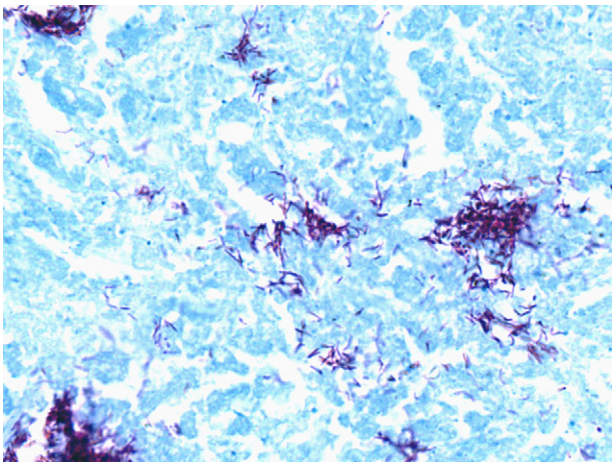

Figure 4 Acid fast organisms in a patient with end-stage lung disease following HCT. Acid-fast stain, 1000×.

(Fig. 4).[135] Based on data from developed countries, mycobacterium tuberculosis infections are rare in HCT recipients.[136,137] However, the incidence of tuberculosis in the HCT population directly reflects its incidence in the general population. In Turkey, where tuberculosis is endemic (35/100,000 population vs. 7/100,000 in the US), tuberculosis was 40 times more common in allo-HCT patients than in the general population.[138] The presence of multidrug-resistant strains of *M. tuberculosis* (indirectly related to the treatment of HIV) is of great concern[139] and has led some programs to maintain a high index of suspicion for tuberculosis and to treat HCT recipients with this complication for longer periods of time, often with multidrug-regimens.[137]

Non-tuberculous mycobacterial (NTM) infections can be either catheter-related or respiratory infections.[140] Mere isolation of NTM on BAL might not be of pathogenic significance unless there is evidence of tissue invasion or concomitant bacteraemia is present. Treatment requires two or three anti-microbials guided by *in vitro* susceptibility testing, and removal of indwelling catheters (if contaminated) as well as surgical debridement of subcutaneous tunnel infection sites.[140]

Legionella pneumophila

Patients undergoing bone marrow and solid organ transplantation are particularly susceptible to *Legionella* spp. infections due to prolonged neutropaenia and abnormalities in cell-mediated immunity. Legionnaires' disease (LD) can be acquired by inhalation of aerosols containing *Legionella pneumophila* or by microaspiration of contaminated drinking water.[141] LD should always be in the differential diagnosis of pneumonia among HCT recipients. Appropriate tests to confirm LD include culturing sputum, BAL, and tissue specimens; testing BAL specimens for legionellae by direct fluorescent antibody, and examining for *Legionella pneumophila* serogroup 1 antigen in urine and performing testing for 5S rRNA PCR of either BAL, urine or serum samples.[142,143]

LATE NON-INFECTIOUS POST-TRANSPLANT COMPLICATIONS

The differential diagnosis of late-onset pulmonary complications extends from the complications listed in the early non-infectious group to include bronchiolitis obliterans (BO), possibly associated with underlying chronic GVHD, bronchiolitis obliterans organising pneumonia (BOOP) and post-transplant lymphoproliferative disorder (PTLD).[34] Additionally, persistent post-BMT pulmonary findings of VOD and IPS continue to occasionally complicate the late post-transplant course.

Bronchiolitis obliterans

Chronic lower airways obstruction is the most common late pulmonary complication following HCT.[4] BO is most commonly associated with evidence of chronic GVHD and is much more common following allogeneic, as opposed to autologous, marrow transplantation. Additional risk factors include early post-transplant viral infection and advanced age of the recipient.[34,144] Fig. 5 demonstrates subepithelial fibrotic changes in the airways, a common pathologic finding in BO. The insidious nature of this process, together with continuing inflammatory changes involving the airways and parenchyma, can result in end-stage lung disease with diffuse areas of bronchiectasis and fibrosis (Fig. 6).[145]

When approaching a patient with potential post-haematopoietic cell transplant BO, the diagnosis is often made based on the clinical presentation of cough, dyspnea, and/or the insidious nature of the presentation. Additionally, there might be changes in lung function testing when screening asymptomatic patients.[146] Overall, up to 10% of recipients of allogeneic transplant recipients will have some degree of BO and chronic airflow obstruction.[147]

Symptoms are generally seen 12–24 months after HCT, but have been described as early as 90 days after transplantation. The primary symptoms reported at clinical presentation include dyspnea, wheezing, and a non-productive cough; fever is not commonly present. The chest radiograph is often normal, although high-resolution lung CT scans might demonstrate some characteristic abnormalities. The most common chest CT findings in BO are a heterogeneous pattern with areas of patchy hyperaeration, areas with bronchial dilatation, and other areas characterized by hypoattenuation or increased density.[148,149] This combination of findings is often referred to as 'mosaic perfusion'; although not pathognomonic, this pattern is highly suggestive for BO (Fig. 7).

Pulmonary function testing is illuminating, with evidence of airflow obstruction as seen by a decrease in FEV_1 and reduction of the FEV1/FVC ratio.[49] The degree of air trapping seen on the CT images might correlate with the pulmonary function abnormality. Confirmatory biopsy to make the diagnosis of BO is rarely indicated based on the sensitivity of these studies.[4,150]

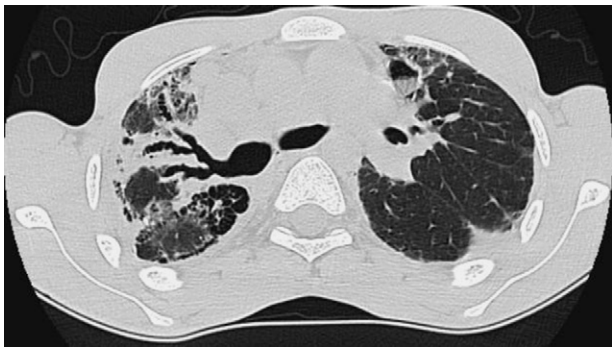

Figure 6 Severe lung disease following HCT as seen on high-resolution CT scan. Note both bronchomegaly and bronchiectasis, seen best in the right upper lobe. Additional findings include widespread fibrosis of the right upper lobe and lingula, with relative sparing of the left lower lobe; pleural thickening is present bilaterally.

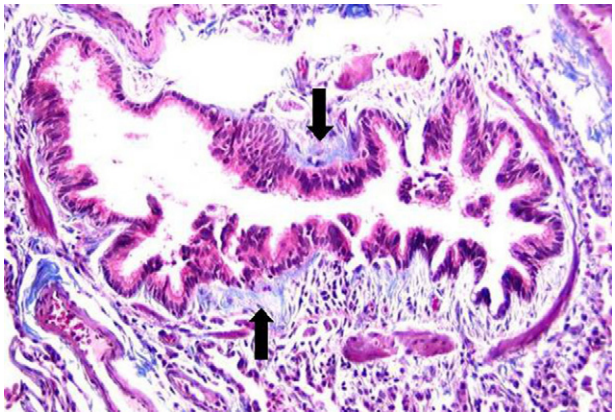

Figure 5 Bronchiolitis obliterans. This photomicrograph of an airway demonstrates subepithelial fibrosis (see arrows). Trichrome stain, 100×.

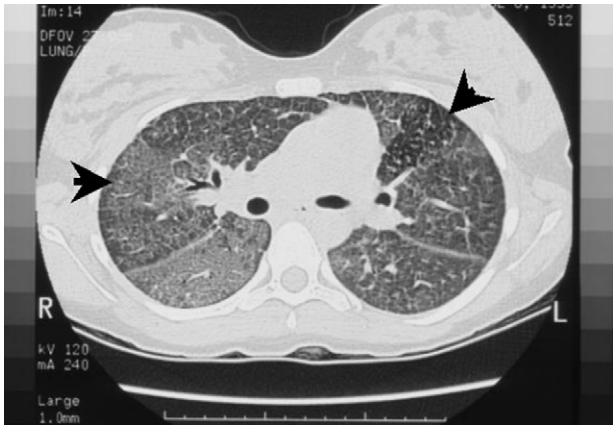

Figure 7 Early changes of bronchiolitis obliterans as seen on a high-resolution CT scan. Note the changes consistent with mosaic perfusion (see arrows), characterized by areas of varying density (differing attenuation).

Chronic GVHD has been associated with BO but no definitive link has been determined. The incidence is variable, with reports ranging from 2 to 20%.[144] The lack of direct evidence of small airway inflammation resulting in BO leads to the implication that donor T-helper-cell alloreactivity causes distal airway epithelial cell injury, which in turn leads to the pathologic changes seen.[149] Patients undergoing aggressive treatment for chronic GVHD, as well as those who had specific conditioning regimens utilising busulfan and irradiation,[147] are most at risk for BO; however, these simply remain recognized associations resulting in an increased incidence of airways obstruction without a defined mechanism.

Therapy for post-hematopoietic cell transplant BO remains centered on augmenting immunosuppression. Calcineurin-inhibitors and azathioprine, as well as steroids, have reduced the decline in lung function and in some instances have shown improvement in a small proportion of subjects.[151] Recent data suggests azithromycin, a macrolide antibiotic may improve lung function in patients suffering from BO post-BMT.[152] Additionally, cycled high-dose corticosteroids have been shown to reduce oxyhaemoglobin desaturation and improve FEV_1 in a small cohort of paediatric patients following transplant.[153]

The benefit provided by these novel therapies might help clarify the mechanism of injury leading to BO following HCT. Because alloreactivity and inflammation have been offered as contributing causes of BO, the clinical approach to treatment has included both anti-inflammatory and immunomodulatory medications. Case reports present effectiveness in reducing BO by the use of immunomodulation or specific cytokine blockade, such as infliximab, which blocks tumour necrosis factor alpha (TNFα).[154] Whether this will be an effective modality for all HCT recipients awaits prospective, multicentre randomised control trials to determine the optimal therapy, not only to evaluate the aetiology of post-HCT BO but also to determine the treatment for this insidious decline in respiratory function.

Interstitial lung diseases

Interstitial lung disease, which presents with a restrictive pattern on pulmonary function testing, has also been reported as a late post-transplant complication. Here, the typical presentation is that of an asymptomatic subject, who on post-transplant monitoring is found to have decline in the vital capacity and/or diffusion capacity for carbon monoxide.[146] Whereas IPS might be the aetiology for these changes, irradiation, chemotherapy, infectious pneumonitis and BOOP all could contribute to these Pulmonary Function Test (PFT) alterations. Despite efforts to develop a good predictive model, these authors were unable to demonstrate any specific covariates that might predict these PFT changes. Also, whether this is similar to delayed pulmonary toxicity syndrome, as described in adults, remains unclear.[155]

Although the diagnosis is often delayed if based on lung function testing alone, certain predisposing conditions should raise awareness of the potential for developing this restrictive pattern. Some of these might extend from the early post-transplant period and include infection and VOD. However, the most common cause remains pre-HCT exposure to cytotoxic drugs and/or irradiation. Alkylating agents, such as CCNU/BCNU, cyclophosphamide, methotrexate and busulfan have all been implicated in causing late pulmonary toxicity including pulmonary fibrosis.[156] Although steroids might result in clinical improvement,[155] full diagnostic studies should be undertaken to rule out deterioration related to known pre-transplant pulmonary causes as well as to rule out infectious aetiologies.

BOOP, now more commonly referred to as cryptogenic organising pneumonia (COP) differs from BO histologically, physiologically and – most significantly – in its response to treatment. It is histologically distinguished by patchy areas of consolidation with polypoid plugs of loose organising connective tissue in the respiratory bronchioles and alveolar ducts.[148] Associated inflammation can be mild to moderate, but the proliferative bronchiolitis is manifest by patchy infiltrates on chest radiograph and by restriction on pulmonary function testing.[4] Unlike many other post-HCT complications, BOOP/COP often improves with corticosteroid therapy. However, it is critical to rule out other post-HCT complications, particularly infections that might cause similar symptoms and pulmonary radiographic changes. For this reason, bronchoscopy with bronchoalveolar lavage as well as open lung biopsy is often required to seek potential infectious causes as well as to document the histopathology of the lung.[150] Additionally, a response to steroids will help to differentiate between BO and BOOP/COP if the diagnosis is obscure despite studies such as bronchoscopy and/or open lung biopsy.[157]

Pulmonary veno-occlusive disease

Pulmonary VOD is an unusual complication post-HCT but is another condition that might present with radiographic changes demonstrating intimal proliferation and fibrosis of the pulmonary venules.[34] Presentation can be similar to other late non-infectious conditions, with dyspnea, hypoxemia, and chest radiographs showing patchy infiltrates.[158] VOD can be progressive and eventually result in pulmonary arterial hypertension, pulmonary edema, and cardiomegaly on chest radiograph. The etiology of post-HCT pulmonary VOD is unknown, although radiation and chemotherapy pretreatment regimens have been implicated; steroid therapy has been attempted, but no consistently effective therapy has been identified.[63]

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) has been reported primarily in allogeneic HCT recipients, with

an increased risk associated with HLA-mismatched patients, T-cell-depleted grafts, and EBV seronegative recipients who receive transplants from EBV seropositive donors.[159] PTLD typically stems from a conditioning regimen that causes T lymphocyte depletion, which then leads to uncontrolled EBV-driven B cell proliferation. This unregulated growth of B cells can range from benign polyclonal B lymphocyte expansion to aggressive, immunoblastic B cell lymphomas.[160] The presentation is usually within the first year of transplantation, with the peak incidence 1–5 months after transplant. Analysis of EBV viral load in the peripheral blood is an integral component of post-HCT monitoring. Screening of the at-risk patient population might be the earliest means of detecting the presence of EBV as a marker for PTLD prior to the onset of clinical symptoms. In those patients who present with clinical disease, nodular abnormalities might be seen on chest radiograph and CT scan and might be associated with areas of consolidation.[158]

First-line therapy for PTLD remains reduction of immunosuppression to reduce the degree of T lymphocyte depletion. This reduction can be associated with further complications and might still be insufficient.[161] Anti-viral agents, intravenous immunoglobulin, and even anti-B cell immunotherapy have been attempted with varying degree of success. Reduction of risk factors and monitoring of T-cell-depletion is critical; novel therapeutic regimens to treat this potentially fatal complication of HCT are being investigated.

Pulmonary alveolar proteinosis

Recent literature has described pulmonary alveolar proteinosis (PAP) in conditions associated with immune impairment, specifically post-HCT. This condition is associated with the excessive accumulation of surfactant lipoprotein in the alveolar space and results in defective air exchange and hypoxemia. Like other non-infectious presentations, bronchoscopy can prove useful if a diagnosis of PAP is suspected. The diagnosis is easily made on BAL, where the distinctive finding is the lipoproteinaceous, milky white fluid recovered from the lower airway. This finding can be subsequently confirmed via laboratory analysis.[4] The treatment for PAP requires the physical removal of this excessive surfactant material, usually by sequential lavage.[162]

FUTURE INVESTIGATIONS

Successful outcomes following HCT remain hampered by the high incidence of pulmonary complications. However, innovative therapies that can reduce lung morbidity following HCT are becoming available. Focusing on immunologic interventions to reduce GVHD and other post-transplant complications appears to be important in reducing pulmonary problems post-HCT. Promising data are being generated from groups addressing tolerance, novel stem cell sources, and medications for the prevention of chronic GVHD.[163,164] Although numerous agents have been tried and have failed to alter the rate of pulmonary complications associated with GVHD, recent interventions have been more hopeful in addressing these issues.[165]

Inducing tolerance has been attempted using a number of different techniques with varying success. To reduce lung injury associated with GVHD, amelioration of the T-lymphocytic response is necessary and a number of techniques have been proposed. Chemotherapeutic agents that are still being investigated include steroids, calcineurin-inhibitors, anti-proliferative agents (e.g. mycophenolic acid), and other non-specific immunosuppressives such as hydroxychloroquine. More innovative therapies and treatments that might be more effective are now targeting cytokine and growth factors including antibodies against specific T-cell receptors.[166]

Targeting cellular responses is likely to be an area of active investigation as a means of reducing respiratory symptoms post-HCT. Already, trials utilising antibodies against molecular targets, including anti-TNFα (infliximab), anti-IL-2 receptor (daclizumab) and anti-CD20 (rituximab) have begun; additional trials supplementing hepatocyte growth factor and keratinocyte growth factor have generated promising data suggesting that improved outcomes might result from these more focused interventions.[167]

Finally, non-myeloablative conditioning regimens might prevent the development of pulmonary toxicity. Although these studies have limited numbers of patients, the findings suggest that a somewhat less aggressive conditioning regimen might reduce the amount of post-transplant pulmonary morbidity. Although GVHD was still present, these results suggest that severe pre-HCT immunosuppression might contribute to the development of pulmonary complications including IPS, DAH, and BOS.[55] Further multicenter studies will help determine which of these more novel therapies are best in diminishing post-transplant respiratory morbidity and mortality.

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