Pulmonary Complications of Malignancies and Blood and Marrow Transplantation

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Abbreviations

AIP	Acute interstitial pneumonitis
ALL	Acute lymphoblastic anaemia
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
ARDS	Acute respiratory distress syndrome
BMT	Bone marrow transplantation
BOOP	Bronchiolitis obliterans with organising pneumonia
BOS	Bronchiolitis obliterans syndrome
CBO	Constrictive bronchiolitis obliterans
cGVHD	Chronic graft-versus-host disease

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CMV	Cytomegalovirus
COP	Cryptogenic organising pneumonia
DAH	Diffuse alveolar haemorrhage
DL_{CO}	Diffusing capacity for carbon monoxide
EBV	Epstein-Barr virus
GVHD	Graft-versus-host disease
HL	Hodgkin lymphoma
IPS	Idiopathic pneumonia syndrome
LCH	Langerhans cell histiocytosis
MPS	Mucopolysaccharidosis
NCPE	Non-cardiogenic pulmonary oedema
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PERDS	Peri-engraftment respiratory distress syndrome
PH	Pulmonary hypertension
PTLD	Post-transplant lymphoproliferative disease
PVOD	Pulmonary veno-occlusive disease
SVC	Superior vena cava

Introduction

Despite improvements in survival among cancer patients and BMT recipients there is still substantial morbidity and mortality) associated with pulmonary complications [1–9]. Pulmonary injury can be complex and multifactorial and thus will be examined in relation to underlying malignancy, infectious and non-infectious etiologies as summarised in Table 1. Toxicity resulting from radiation therapy is described in chapter "Pulmonary Complications of Radiation Therapy".

Table 1 Classification of common complications of childhood cancer affecting the chest [1–3]

Malignancy	Infections	Non-infectious and immune
Primary and metastatic tumours Pulmonary infiltrate from systemic disease Leukemic and lymphomatous involvement – Hyperleukocytosis and pulmonary leukostasis – Acute lysis pneumopathy Superior vena cava and superior mediastinal syndrome	Impaired immune function Bacterial Viral Fungal	Drug or radiation toxicity – Acute hypersensitivity reactions – Interstitial pneumonitis – Pulmonary fibrosis – Acute respiratory distress syndrome Pulmonary embolism Pulmonary oedema Alveolar haemorrhage Acute capillary leak syndrome Graft-versus-host disease Impaired growth and development

Pulmonary Malignancies and Complications of Treatment

Complications Directly Resulting from Malignancy

Primary and Metastatic Lung Tumours

Primary lung tumours are extremely rare, representing only 0.2% of all childhood cancers [4, 5]. The vast majority of pulmonary malignancies are in fact metastases, characteristically located in peripheral lower lung segments as well-circumscribed nodules and most commonly associated with Wilm's tumour and osteosarcoma [4–6]. While parenchymal lesions exhibit a more insidious and non-specific presentation, endotracheal and endobronchial lesions often present with unilateral wheeze due to obstruction and can be easily misdiagnosed as asthma [7]. Despite the rarity and non-specific clinical presentation of most lung tumours, malignant disease should be considered in children with constitutional symptoms and persistent wheeze, haemoptysis, atelectasis or pneumonia who fail to respond to therapy [5].

Pulmonary Infiltrates from Systemic Disease

Hyperleukocytosis and Pulmonary Leukostasis

Hyperleukocytosis, defined by a leukocyte count greater than 100×10^9/L, occurs in up to 20% of initial presentations of acute lymphoblastic leukaemia (ALL) and 15% of acute myeloid leukaemia (AML) [1, 8]. Excess leukaemic aggregates can lead to pulmonary leukostasis, a life-threatening complication where cellular occlusion of the pulmonary vasculature leads to hypoxia and acute respiratory distress [9, 10]. While this condition only occurs in up to 6% of children with acute hyperleukocytic leukaemias, associated respiratory failure is one of the most common causes of early mortality in this setting [11, 12].

The pathophysiological basis of hyperleukocytosis-induced pulmonary leukostasis is related to the stasis of hyperviscous blood from elevated leukocrit [1]. Aggregates of rigid blasts cause plugging of the microvasculature and associated oxygen defects, potentiating pulmonary endothelial injury, haemorrhage and tissue hypoxia [8, 13, 14]. As such, the risk of respiratory complications increases with the degree of leukocytosis [15]. However, not all children with high leukocyte counts, such as those with chronic leukaemias, develop this complication due to the morphology and maturity of the leukocytes. Children with AML are at greatest risk of pulmonary leukostasis and tend to develop respiratory distress at lower leukocyte counts than those with ALL [9, 12]. This is because myeloblasts are larger and release pro-inflammatory cytokines with specific adhesion molecules that facilitate aggressive invasion of pulmonary endothelium [12, 16].

Pulmonary leukostasis is empirically diagnosed when children with leukaemia present clinically with hyperleukocytosis and respiratory distress. Though often

non-specific, it can manifest in dyspnoea, pleuritic chest pain and hypoxaemia and lead to right ventricular failure [17]. Chest X-rays may be normal or may show alveolar consolidation and diffuse reticulonodular infiltrates that may resemble pneumonia or interstitial oedema [18]. Computed tomography (CT) radiography may demonstrate thickening of the bronchovascular bundles, prominence of peripheral pulmonary arteries and ground-glass opacities due to leukaemic cell infiltration [1, 17, 18]. Definitive management remains controversial; however, hyperhydration, urate oxidase, low-dose chemotherapy and consideration of leukopheresis may be beneficial in children with extremely high leukocyte counts [12, 15, 19].

Acute Lysis Pneumopathy

Upon initiation of chemotherapy, children with severely worsening hypoxaemia may be symptomatic of 'acute lysis pneumopathy'. This is a rare complication of myelomonocytic and monocytic leukaemias, where lysis of leukaemic cells trapped in the lungs causes diffuse alveolar damage [3, 20, 21]. Management considerations include temporary discontinuation of chemotherapy, steroids and transfusions [22, 23].

Pulmonary Infiltrate in Leukaemia and Lymphoma

Outside the context of hyperleukocytosis, post-mortem evidence has also found diffuse and focal leukaemic infiltration of lung parenchyma, pleura, alveoli, bronchi, and pulmonary vessels in patients with leukaemia and lymphoma [24, 25]. However, symptomatic pulmonary disease due to isolated leukaemic cell infiltrates is uncommon [3, 26].

Langerhans Cell Histiocytosis (LCH)

Pulmonary involvement in LCH occurs in up to 50% of children with multisystem disease and very rarely as primary pulmonary LCH [2, 27–29]. Pathologic accumulation of Langerhans cells admixed with eosinophils, macrophages, and T lymphocytes typically exhibits a bronchocentric infiltration pattern [5, 30]. This is best assessed on high-resolution CT, typically showing reticulonodular opacities in the mid to upper zones with sparing of the costophrenic angles [29, 31]. With progressive destruction of the bronchioles, lesions develop more a diffuse, cystic and fibrotic 'honeycombing' appearance [2, 31].

Extra-Pulmonary Tumours

Mediastinal tumours can compress the tracheobronchial tree and pulmonary vessels causing respiratory insufficiency, superior vena cava (SVC) syndrome and/or superior

mediastinal syndrome [1, 6]. The low intraluminal pressure and delicate wall of the SVC in children with smaller thoracic capacity renders it particularly vulnerable, especially to rapidly enlarging masses of haematological malignancies such as Hodgkin lymphoma, T-cell leukaemia and germ cell tumours [1]. Respiratory manifestations include cough, stridor, chest pain, dyspnoea, orthopnoea, and aversion to the prone position [11]. In these children at risk of cardiorespiratory collapse, urgent assessment of haemodynamic compromise and airway patency such as with a prone CT is essential.

Extra-thoracic space-occupying tumours such as Ewing's sarcoma can also impair normal diaphragmatic excursion and mechanically compromise the respiratory system [1]. Rarely, intracranial tumours can lead to central hypoventilation syndromes or sleep apnoea [1, 2].

Infectious Complications and Their Relationship to Immune Function

Malignancy and cytotoxic therapies cause multifactorial immune defects (Fig. 1) including severe myelosuppression, multi-organ dysfunction and compromise of the mucosal integrity of the respiratory system [35]. Thus, children with cancer undergoing chemotherapy are at high risk of infections from typical and opportunistic viral, bacterial and fungal pathogens (Table 2) [39, 40]. Respiratory infections carry significant morbidity and mortality, particularly during severe neutropenia and intensive induction therapy [41]. Infection-related acute respiratory failure has been reported as a common cause of ICU admission and mortality in paediatric oncology [1, 42].

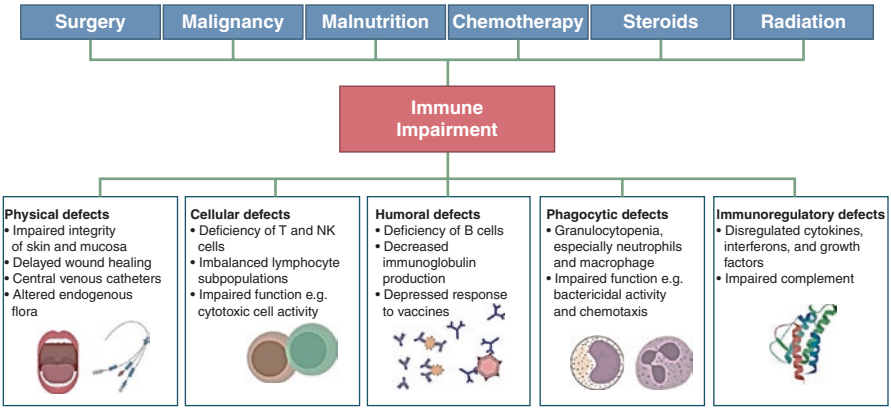

Fig. 1 Immune defects due to malignancy and cytotoxic therapy [32–34]

Table 2 Common respiratory pathogens in childhood malignancy [1, 24, 36–38]

	Common organisms	Risk factors
Protozoa	*Toxoplasma gondii*	Lymphopenia
Fungi	*Aspergillus species* *Candida* *Zygomcetes* *Pneumocystis jiroveci*	Chronic immunosuppression Severe neutropenia <100/μL Prolonged neutropenia >7 days High-dose corticosteroids
Viruses	Respiratory syncytial virus, rhinovirus, influenza, parainfluenza, human metapneumovirus, adenovirus, cytomegalovirus, varicella zoster, herpes simplex	Lymphopenia Young age < 2 years old
Bacteria	*Pseudomonas, Mycoplasma, Legionella, Chlamydia, Mycobacteria, Haemophilus influenzae* *Streptococcus, Staphylococcus*	Neutropenia, 7–12 days post-chemotherapy Skin infections

Table 3 Differentials for pulmonary infiltrates found in childhood malignancy

Pulmonary infiltrate	Differentials/causes
Local	Infection—bacterial (early) or fungal (late) Tumour Pulmonary embolus
Diffuse	Systemic disease infiltrate (Langerhan cell histiocytosis, leukaemia, lymphoma) Pulmonary haemorrhage Cardiogenic and non-cardiogenic pulmonary oedema Pulmonary leukostasis Diffuse alveolar damage Viral pneumonia Drug or radiation toxicity
Late	Immune reconstitution resulting in fibrosis Pneumocystosis

In a neutropenic child, pulmonary infections can be subclinical due to immune failure to mount an inflammatory exudative response [39, 43, 44]. Chest radiography can also be normal, with studies suggesting it is only useful for evaluating a symptomatic child or monitoring treatment response [43, 45]. While bronchoalveolar lavage is a valuable diagnostic tool, it may be of less value if patients have already commenced empirical broad-spectrum antimicrobials [46]. CT-guided fine-needle biopsy can also play a role; however, the gold standard remains thoracoscopic or open lung biopsy [47]. This is usually reserved for diagnostically challenging cases that are non-responsive to therapy. Of note, a wide range of differentials of pulmonary infiltrates can also mimic infections (Table 3) [48].

While respiratory infections are a common cause of fevers in children with cancer, their long-term pulmonary sequelae remains unclear. In childhood leukaemia survivors, reduced lung volumes and impaired exercise capacity have been correlated with recurrent chest infections [49]. Impaired cellular and humoral immune function have also been found to persist >1 year post-therapy depending on treatment intensity [44, 50].

Non-Infectious Complications

Chemotherapy

The respiratory system is particularly susceptible to drug toxicity during childhood due to ongoing physiological development, its rich vascularity and large contact surface area. As summarised in Table 4, the presentation and pathogenesis of injury varies with specific drugs but is generally hypothesised to arise from several key mechanisms: (1) oxidative injury to endothelium and pneumocytes, (2) cytokine induction and inflammation, (3) proteinolytic destruction, (4) immune dysregulation and/or (5) idiosyncrasy [35, 55–57].

Pulmonary-toxic chemotherapies can cause acute pulmonary and pleural reactions such as hypersensitivity pneumonitis, pleural effusions and lung infiltrates. Hypersensitivity reactions are most frequently reported with bleomycin and methotrexate and usually manifest as reversible eosinophilic or desquamative interstitial

Table 4 Common chemotherapeutic agents associated with pulmonary complications [2, 51–54]

Drug class	Key agents	Main uses	Pulmonary complication
Antibiotics	Bleomycin Doxorubicin	HD, lymphomas Germ cell tumours	Hypersensitivity pneumonitis, interstitial pneumonitis Pulmonary fibrosis, ARDS
Alkylating agent	Busulfan Melphalan Cyclophosphamide Ifosfamide	BMT BMT Widely used	Late-onset pulmonary fibrosis Early- or late-onset pneumonitis, bronchospasm, diffuse pulmonary haemorrhage
Nitrosoureas	BCNU (carmustine) CCNU (lomustine)	BMT, CNS tumours	Pulmonary fibrosis
Antimetabolite	Methotrexate Mercaptopurine Cytarabine Gemcitabine	ALL, non-HL ALL AML, non-HL HD	Hypersensitivity pneumonitis, interstitial and alveolar infiltrate, pleural effusion Capillary leak syndrome, NCPE NCPE, capillary leakage, diffuse alveolar damage and haemorrhage, ARDS
Plant alkaloids	Vinblastine Vincristine	ALL, lymphoma Low-grade glioma	Bronchospasm Neurotoxicity-related vocal cord paralysis and airway compromise
Newer agents	Rituximab	Lymphoma, post-transplant lymphoproliferative disease	Acute interstitial pneumonia, lung fibrosis
	Transretinoic acid	APL	Retinoic acid syndrome, diffuse pulmonary infiltrate
	Taxanes	Experimental	Interstitial pneumonitis, diffuse alveolar damage Pleural effusion

pneumonitis [48, 55, 58]. However, the most pertinent and concerning pulmonary complications of chemotherapy are interstitial pneumonitis and permanent fibrosis. These have been found to cause premature mortality, impaired diffusion, and limited exercise capacity in adult life [2, 58]. While children may be asymptomatic during treatment, persistent subclinical abnormalities indicate potential for decompensation with ageing [59].

In the absence of pathognomonic findings, drug-induced lung toxicity is a diagnosis of exclusion [1]. Typical features include:

- Clinical signs and symptoms of hypoxaemia, dry cough, crackles, and exertional dyspnoea
- Restrictive pattern on pulmonary function testing and impaired diffusion capacity [56]
- Diffuse alveolar or interstitial infiltrates on CT imaging
- Interstitial thickening, chronic inflammatory cell infiltrate (including eosinophils in hypersensitivity reactions), and type 2 pneumocyte hyperplasia on pathology [2, 35, 51]

Hyperinflation and obstructive defects secondary to airway inflammation and oedema may also be observed [1].

Specific offending agents are difficult to isolate in polytherapeutic regimes. Synergistic toxicity has been observed when specific chemotherapies are combined with radiation therapy (e.g., bleomycin, busulfan) or oxygen (bleomycin). Furthermore, certain drug combinations, particularly nitrosoureas and cyclophosphamides, can potentiate toxicity at lower doses [60].

Management is primarily reactive with cessation of the offending chemotherapy agent and supportive care with bronchodilators, antibiotics, airway clearance and/or supplemental oxygen [2, 61]. Limited evidence suggests corticosteroids may relieve hypersensitivity reactions, though steroid withdrawal must be gradual to avoid reactivation [55, 61]. Early drug-induced pneumonitis is largely reversible, emphasising the importance of lung function monitoring and prompt diagnosis [55, 62]. However, pulmonary function and radiographic abnormalities often persist into adulthood and are associated with premature lung disease and mortality [2, 58, 59, 62].

Bleomycin is a cytotoxic antibiotic used for paediatric lymphomas and germ cell tumours. It is the most widely recognised cause of drug-related lung injury, affecting up to 72% of children treated with bleomycin with a 1–2% mortality [58, 61–66]. Bleomycin has been reported to cause both acute hypersensitivity reactions and late interstitial pneumonitis and fibrosis within 1 year of treatment [55, 67, 68]. Vascular toxicities involving intimal fibrosis and pulmonary hypertension have also been observed [73].

The pathogenesis of bleomycin lung toxicity primarily involves oxidative damage to cell DNA by free radicals from bleomycin-Fe complexes [69–71]. In the absence of its detoxifying enzyme, bleomycin hydrolase [72, 73], bleomycin can accumulate in the lungs to cause proteolysis of lung parenchyma and direct endothelial injury. Subsequent vascular permeability results in interstitial oedema and the formation of hyaline membranes as plasma proteins and fluid enters alveoli [2]. Cytokines (primarily TNF-α, IL-1B and TGF-B) further potentiate endothelial damage and type 1 pneumocyte apoptosis [61, 74, 75]. Finally, inflammatory cell influx

and immune processes lead to fibrosis of the lung parenchyma and bronchi [2]. Tissue pathology has revealed type 2 pneumocyte hyperplasia, haemorrhage and oedema consistent with diffuse alveolar damage [55].

Important iatrogenic risk factors for bleomycin-induced pulmonary toxicity include cumulative doses greater than 400 IU/m^2, concomitant radiotherapy, high-dose oxygen therapy and certain chemotherapies (cyclophosphamide, vincristine, doxorubicin, cisplatin, methotrexate) [62]. Younger children and patients with impaired renal function limiting drug excretion are at greater risk and need to be monitored with higher caution [35, 58, 71, 76].

Patients with acute toxicity typically present with exertional dyspnoea and a dry cough. Reduced DL_{CO} is considered the most sensitive marker of bleomycin-induced fibrosis, where therapy cessation is indicated if <60% of baseline [2, 62]. However, it is important to note that DL_{CO} abnormalities may only become apparent 6 months post-therapy. CT radiography can be a useful adjunct for monitoring disease progression and typically demonstrates fine nodular infiltrates with a bibasilar reticular pattern [55]. While bleomycin injury is generally associated with restrictive defects and impaired diffusion, a recent study in children treated with contemporary, lower-dose bleomycin regimens found hyperinflation and obstructive lung disease to be most common up to 12 years post-diagnosis [2, 65, 66]. It has been hypothesised that these abnormalities could be due to airway inflammation from bleomycin-induced pro-inflammatory cytokines or a bridging process of early fibrosis.

Alkylating agents are a broad class of chemotherapies known to cause chronic lung injury. In children undergoing pre-BMT conditioning, busulfan can cause acute pneumonitis and alveolar haemorrhage but is most recognised for insidious pulmonary fibrosis up to 10 years post-therapy [71, 77–79]. Typical pathological findings include type 2 pneumocyte hyperplasia and lymphocyte and plasma cell infiltrate. Busulfan-induced fibrosis is typically associated with higher mortality as compared to other chemotherapies, though it does not appear to be dose related [80].

Nitrosoureas are alkylating and carbamylating agents with established dose-dependent pulmonary toxicity. Injury occurs in 50% of those with cumulative doses greater than 1500 mg/m^2 and can manifest as early as 1 month into therapy. Late-onset fibrosis has also been reported in 20–30% of BCNU-treated patients [76] and is associated with significant premature mortality [58].

Cyclophosphamide injury occurs through lipid peroxidation of phospholipid membranes and free radical formation like bleomycin [71]. Toxicity predominantly presents as early-onset pneumonitis within 6 months of exposure and is reversible with drug cessation and steroid therapy [2, 58]. Less than 1% of patients exhibit late-onset pneumonitis that progresses to fibrosis [35].

Surgery

Surgical interventions for lung tumours include pneumectomy, lobectomy, pulmonary metastasectomy and wedge resection [81–83]. Few studies to date have examined post-surgical pulmonary dysfunction in the context of paediatric malignancies. However, virtually all paediatric case series demonstrate good

long-term outcomes even with aggressive surgery in early childhood [84–86]. It is hypothesised that preserved lung function and capacity post-resection are due to hyperplastic compensatory mechanisms and hyperinflation of remaining tissue [87–89].

Complications of thoracic surgery, however, may include irreversible airway obstruction due to dysanapsis [84, 90], diaphragmatic hernia or phrenic nerve injury [91] and post-pneumonectomy syndrome due to herniation of flexible mediastinal structures into a vacant pleural cavity [88]. Progressive hyperinflation can lead to bronchomalacia and predispose to pulmonary infections [92, 93]. Damage to the chest wall and musculoskeletal deformities, particularly scoliosis, can also restrict thoracic excursion and pulmonary growth and function [94]. Thus, both functional lung testing and imaging are essential in follow-up and management.

Thromboembolic Complications

Pulmonary embolism (PE) is a rare but life-threatening complication that has been reported in 1.9–4.5% of paediatric oncology patients [95–97]. While the etiopathogenesis is difficult to determine, thromboembolic events may be associated with increased thrombin generation with malignancy, tumour emboli from cell lysis, altered haemostasis due to L-asparaginase use, acquired thrombophilia in the early post-transplant period, thrombogenic intravenous hyperalimentation and/or endothelial injury with central line use [98–100]. In children with acute respiratory failure associated with PE, studies suggest prompt thrombolytic therapy is effective for reducing early morbidity [95]. However, asymptomatic and undetected PEs do not appear to adversely affect patient outcomes [97].

Growth and Development

Children undergoing cancer treatment inevitably suffer significant disruption to normal lung growth and development due to surgery, cytotoxic therapy, chronic immunosuppression, prolonged steroid use and nutritional stress [101]. Children are at risk of impaired alveoli development, which can lead to respiratory insufficiency [102, 103]. Abnormal growth of musculoskeletal structures can also decrease chest wall compliance and further restrict pulmonary function [58]. Other respiratory morbidities can be associated with cardiopulmonary compromise, limited exercise tolerance and infections due to delayed immune reconstitution. Notably, studies have found the cumulative incidence of pulmonary morbidities increases with time since diagnosis [59]. This suggests that early childhood injury may cause late-onset respiratory complications and potentially accelerate physiological lung function decline.

Pulmonary Complications of Blood and Bone Marrow Transplantation

Since the first reported successful application of blood and bone marrow transplantation (BMT) to treat leukaemia in 1959 [104], BMT has been increasingly utilised across a range of conditions with high mortality rates [105]. Despite advances in BMT over recent decades [106], pulmonary complications continue to be a significant cause of ongoing morbidity and mortality [101]. Pulmonary complications are estimated to occur in 25% of paediatric post-BMT patients and are associated with a close to 50% increase in risk of mortality [101, 107]. Long-term follow-up studies of BMT survivors have documented the occurrence of both obstructive and restrictive lung disease following transplantation [108–110].

Multiple mechanisms are responsible for post-BMT pulmonary injury. Damage resulting from chemotherapy (including conditioning agents busulfan and cyclophosphamide) [59] has been discussed previously in this chapter, and lung injury resulting from irradiation is described in chapter "Pulmonary Complications of Mental Health Problems". Additional mechanisms through which lung injury occurs include immune-mediated events (e.g., graft-versus-host disease) as well as effects of ongoing immunosuppression [101]. A tri-phasic model of injury for chronic lung injury post-BMT has been proposed, and steps include:

1. Alloantigen recognition occurs and inflammatory cells proliferate.
2. Persistence of the inflammatory phase causes lymphocyte migration into the mucosa of the airways and result in epithelial cell damage.
3. Proliferation of lung fibroblasts then increases production and deposition of collagen [111].

Post-BMT pulmonary complications can be categorised into infectious and non-infectious complications and further separated into early (in the first 100 days post-BMT) and late (after 100 days post-BMT) as shown in Table 5 and Fig. 2. Infectious

Table 5 Infectious and non-infectious pulmonary complications post-BMT according to timing post-transplantation [112, 113]

	Infectious complications	Non-infectious complications
0–100, days, early-, post-BMT	Bacterial infections Fungal infections Pneumocystis jirovecii New community viral infections Viral reactivation—cytomegalovirus (CMV), Epstein-Barr virus (EBV)	Acute graft-versus-host disease Mucositis Pulmonary oedema Idiopathic pneumonia syndrome Pulmonary veno-occlusive disease
Late >100 days post-BMT	Late viral infections—adenovirus, HHV-6, human metapneumovirus (HMPV) Mycobacterial disease Atypical pneumonia—Legionella	Graft-versus-host disease (GVHD) Interstitial lung disease Post-transplant lymphoproliferative disease (PTLD) Bronchiolitis obliterans syndrome (BOS)

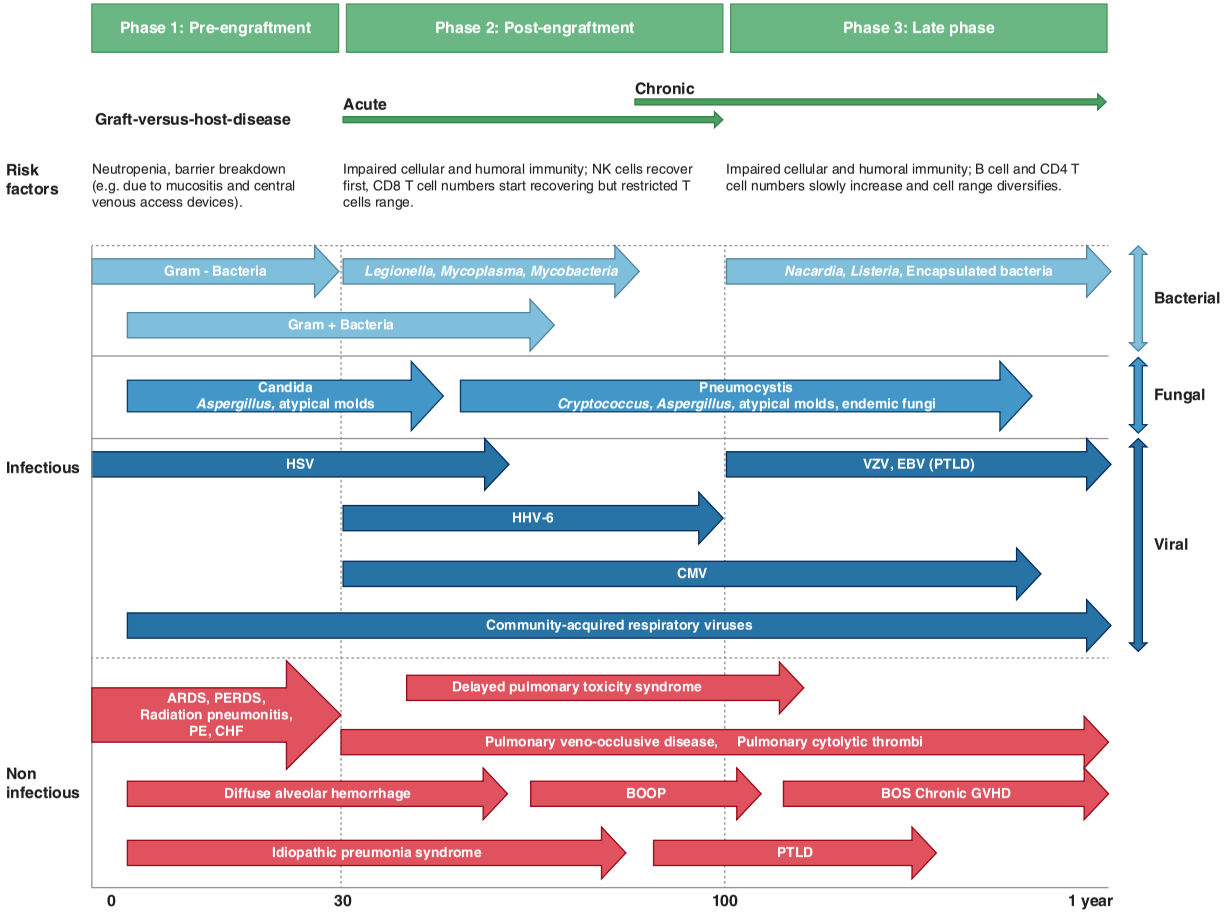

Fig. 2 Pulmonary complications post-BMT categorised to site of injury [109, 114]

complications play an important role in the first months following transplantation, and non-infectious aetiologies play a more prominent role in the months and years after BMT [101]. Another classification system is based on the site of lung injury: lung parenchyma, airway epithelium and vascular endothelium as shown in Fig. 3 [101].

Infectious Complications and Their Relationship to Immune Function

Infectious complications are common post-BMT and can occur in allogeneic and autologous recipients. However, they are more common in allogeneic transplant recipients, and this is believed to be secondary to GVHD and immunosuppressive medication use [115]. Additional known risk factors for infection post-BMT include allogeneic transplant, HLA mismatch, more advanced disease prior to BMT, unrelated donors, immunosuppression, high-dose chemotherapy/radiotherapy for conditioning and delayed engraftment [106].

The infectious complications occurring in post-transplant can be classified by time post-transplant according to the following three phases:

1. Phase 1—The pre-engraftment stage (up to 30 days post-BMT) includes the time in which the neutrophil count recovers.
2. Phase 2—Post-engraftment phase (30–100 days post-BMT).
3. Phase 3—The late phase (>100 days post-BMT) [106, 112, 115].

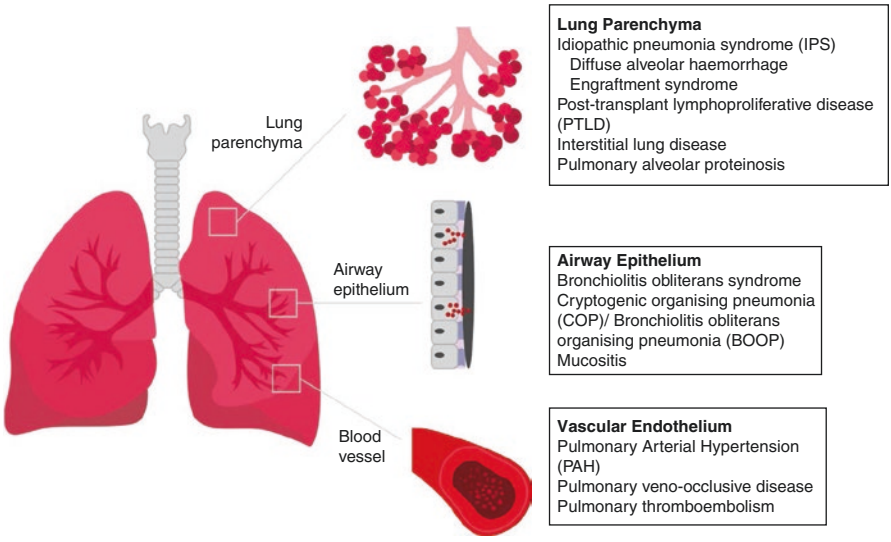

Fig. 3 Timeline of infectious and non-infectious complications post-BMT. Figure adapted from [106, 115, 116]

During the pre-engraftment phase, neutropenia and interruption of the mucocutaneous barrier place patients at risk of bacteraemia as well as fungal infections (mould and yeast species) [112, 115]. *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* are important gram-negative organisms, which causes bacteraemia in the pre-engraftment stage. *Staphylococcus aureus*, *Streptococcus viridans* and *Enterococcus* spp. are the common gram-positive organisms seen in this phase [115, 117].

Infections during the post-engraftment phase are predominately related to deficiencies in cell-mediated immunity. Additional risk factors are graft-versus-host disease and immunosuppressive therapy. The major pathogens during this phase are the herpes viruses (especially CMV and EBV), *Pneumocystis jirovecii* and *Aspergillus* species.

The late phase involves gradual immune system rebuilding as well as the tapering of immunosuppressive agents [112]. During this time the primary pathogens are CMV, EBV, adenovirus and encapsulated bacteria (e.g., *Streptococcus pneumoniae*). GVHD severity is again a risk factor for infection in this phase [106]. Though opportunistic infections rarely occur late post-BMT, cases are reported which suggests that transplantation itself (in the absence of GVHD or immunosuppression) can cause long-term immune dysfunction [115]. One of the factors influencing this is that for restoration of humoral immune function, post-BMT rebuilding of stores of naïve B cells and memory B cells is necessary. Hence all BMT patients are at risk of opportunistic infections from encapsulated bacteria and viruses for up to 1 year post-BMT [115].

Non-Infectious Complications

Mucositis

Oral mucositis is a well-known and common early complication affecting the majority of patients undergoing BMT [112]. Mechanisms resulting in development of mucositis include intensive chemotherapy, irradiation, bacterial colonisation, increased inflammatory cytokine and oxidative stress [118]. Compromised mucociliary clearance then leads to the development of respiratory pathology such as sinusitis, oropharyngeal haemorrhage and aspiration pneumonia. In more severe cases, it can result in upper airway obstruction due to laryngeal or epiglottic oedema [112].

Pulmonary Oedema

Pulmonary oedema is a common post-BMT complication and typically occurs in the second or third week post-transplantation [113]. Possible mechanisms for development include increased hydrostatic pressure (from intravenous rehydration or parenteral nutrition), cardiac dysfunction (anthracyclines), nephrotoxicity (cyclosporin), increased pulmonary capillary permeability (sepsis) or pulmonary toxicity

(chemotherapy or irradiation) [112]. Clinical findings are typical of those seen in pulmonary oedema affecting non-BMT patients dyspnoea, tachypnoea and hypoxia. Radiography may show bilateral infiltrates, Kerley B lines and pleural effusions. Diuresis remains the mainstay of treatment [113].

Immune-Mediated Phenomena

Idiopathic pneumonia syndrome (IPS) typically occurs in the peri-engraftment period, weeks to months after BMT [114]. The definition of IPS has recently been updated in an American Thoracic Society (ATS) Research Statement [114]. The ATS now defines IPS as "an idiopathic syndrome of pneumopathy after BMT, with evidence of widespread alveolar injury and in which infectious aetiologies and cardiac dysfunction, acute renal failure or iatrogenic fluid overload have been excluded" [114]. The clinical presentation of IPS is with dry cough, hypoxia and increasing dyspnoea. The incidence in paediatric BMT is estimated at 5–10%, and the reported mortality approaches 75% [119, 120]. The pathophysiology of IPS is still not well understood; however, the most likely factors at play are cytotoxic and immune-mediated insults to the lungs [114]. Biopsy is often not possible due to the clinical instability of patients as well as the high mortality risk of the procedure in early transplant [113, 114]. Current treatment includes supportive care and systemic corticosteroid therapy [101, 114].

Clinical entities included in the IPS definition are acute interstitial pneumonitis (AIP), diffuse alveolar haemorrhage (DAH) and peri-engraftment respiratory distress syndrome (PERDS) [101, 114]. DAH begins in the pre-engraftment period (most commonly in the second or third week) [113], and a higher rate of DAH is seen in patients with mucopolysaccharidosis (MPS) [118]. Typical clinical features are increasing dyspnoea, dry cough, and hypoxaemia [113]. Fevers may or may not occur. Bronchoalveolar lavage (BAL) reveals increasingly blood-stained fluid; however, haemoptysis is not typically seen [114]. PERDS develops in the first 5 days post-engraftment during neutrophil recovery [114] [121]. Classically patients present with fever, rash and hypoxaemia and dyspnoea due to non-cardiac pulmonary oedema [121]. PERDS has been observed in non-myeloablative regimens that avoid conditioning-associated toxicities. This would suggest that white cell recovery itself and the associated release of soluble factors are implicated in the aetiology of PERDS [121].

Graft-versus-host disease (GVHD), an immune-mediated disease, plays an important role in complications in multiple organ systems in BMT recipients [122]. Lung biopsy is not often performed in BMT patients, and therefore the extent of GVHD and level of pulmonary tissue damage are not as clearly understood as that of other organ systems [122]. Historically the lungs were not believed to be a typical target for acute GVHD; however, data now reveals that this is the case for a subgroup of patients [122]. Recent National Institute of Health (NIH) working groups have sought to better define lung chronic GVHD [123, 124]. Previously, the only diagnostic pulmonary manifestation of cGVHD was biopsy-proven constric-

tive bronchiolitis obliterans (CBO); however, bronchiolitis obliterans syndrome (BOS), a clinical entity, is now included in the NIH diagnostic criteria for lung cGVHD [123].

BOS is the most common late pulmonary complication and the most common obstructive lung disease in BMT patients [109, 110, 112]. BOS occurs in 4–9% of the paediatric post-BMT population [109] with mortality reported to range from 11% to 67% [109, 125]. Symptoms of BOS typically present months after BMT and include cough, wheeze and exertional dyspnoea [109, 125]. The diagnosis of BOS is largely based on high-resolution computed tomography (HRCT) findings (air trapping and mosaic attenuation) and an obstructive pattern on pulmonary function testing (PFTs). Confirmatory lung biopsy is not commonly required [101, 112]. The proposed NIH criteria for lung GVHD are:

1. FEV1/FVC < lower limit of normal
2. FEV 1 < lower limit of normal with ≥10% decline over less than 2 years
3. Absence of respiratory infection
4. Evidence of gas trapping on PFTs or air trapping, small airway thickening or bronchiectasis on HRCT

In the presence of distinctive GVHD of another organ system, the fourth criteria does not need to be met. If BOS is the only manifestation of cGVHD and no other organ system is involved, then a lung biopsy is necessary for diagnosis [123].

CBO is a pathological diagnosis and is otherwise known as bronchiolitis obliterans or obliterate bronchiolitis by clinicians [126]. It is caused by fibrosis and subsequent obliteration of the peripheral airway lumen due to insults such as viral infections, immune reactions from transplanted immune cells and drug toxicity [101]. Risk factors for development in post-BMT populations include chronic graft-versus-host disease (cGVHD), pre-transplant conditioning (e.g., busulfan), early viral infections and advanced age of recipient [112]. Treatment involves immunosuppression using oral and inhaled corticosteroids. Other medications which may have a role include azithromycin used for its anti-inflammatory properties and monoclonal antibodies such as rituximab [112]. A wide range of non-steroidal immunosuppressive agents have also been used including azathioprine, mycophenolate mofetil, calcineurin inhibitors, imatinib, and etanercept [127]. In treatment-resistant disease, lung transplantation has been used [109].

In CBO the fibrotic obliteration of the bronchiolar airways begins externally to the airway lumen resulting in concentric constriction and finally obliteration of the airway lumen [126]. Hence CBO is a peri-bronchiolar fibrotic process, and it can be a patchy disease making biopsy difficult [126]. While the clinical BOS classification includes CBO, BOS also encompasses other pathological entities such as lymphocytic bronchiolitis (LB) [124, 128]. In LB, lymphocytic inflammation occurs around and infiltrates the peripheral airways; however, there is no sub-epithelial fibrosis. It has been proposed that LB may be an earlier stage in the development of CBO from several differing underlying disorders including infection [129]. CBO and LB patients present with similar clinical symptoms and have similar pulmonary function; however, those with LB respond better to treatment [128]. Bronchiolitis

obliterans with organising pneumonia (BOOP), now also called cryptogenic organising pneumonia (COP), is a separate clinical and histological entity and is described later in this chapter [124].

Post-transplant lymphoproliferative disorder (PTLD) is a potentially fatal complication of both BMT and solid organ tumours. The risk of PTLD in BMT is lower than that in solid organ transplant, and the incidence is reported to be 0.5–1% [122, 130]. It is most commonly reported in allogeneic transplant recipients, and risk factors are HLA mismatch, T-cell-depleted grafts and EBV-seronegative recipients matched with EBV-seropositive donors [131]. Conditioning protocols that result in T-cell depletion and in turn cause uninhibited EBV-driven B-cell production are implicated in PTLD. PTLD can be classified into four pathogenic categories:

1. Early lesions including reactive plasmacytic hyperplasia (PH) and infectious mononucleosis (IM)-like PTLD
2. Polymorphic lesions which show disruption of nodal architecture or a destructive extra-nodal mass
3. Monomorphic PTLD which can be divided into B-cell or T-cell neoplasms
4. Hodgkin lymphoma (HL) which is an unusual form of PTLD with histology similar to classic HL [132]

The clinical presentation is typical in the first year of BMT, and monitoring of EBV viral load is important in BMT patient surveillance. Imaging often shows nodular lesions on chest X-ray or CT scan [112]. The first-line mainstay of PTLD treatment is the reduction in immunosuppression. Additional therapeutic measures typically used are anti-B-cell immunotherapy (rituximab), chemotherapy, radiotherapy and intravenous immunoglobulin [132].

Endothelial Injury

Chemotherapy agents and radiation therapy used in conditioning pre-transplantation can cause vascular inflammation and endothelial activation [133]. Endothelial activation can in turn contribute to the downregulation of anticoagulant (e.g., antithrombin, protein C and S) and anti-inflammatory molecules resulting in thrombosis and fibrogenesis [134]. Endothelial damage causes a reduction in the production of endogenous vasodilators (e.g., nitric oxide and prostaglandin I_2) and hence results in vasoconstriction [135].

Pulmonary hypertension (PH) post-BMT was first described in 1984 and has been subsequently described in a number of case series and is believed to be rare; however, the incidence in current BMT recipients is unknown [136]. The two entities of PH commonly described are pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (PVOD) [137]. PH in the setting of BMT may also occur secondary to left-sided heart disease, interstitial lung disease, thromboembolism, and hypoxia [138]. It is most described in allogeneic transplant for malignant infantile osteopetrosis [139].

Pulmonary arterial hypertension (PAH) is more commonly reported and involves the pulmonary arterioles. Clinically patients may be asymptomatic early in disease or may report non-specific symptoms such as fatigue or exertional dyspnoea. Pulmonary vasoconstriction plays an important early role, and a progressive increase of pulmonary arterial vascular resistance causes right ventricular failure [136, 138]. On histopathology, vascular proliferation and remodelling is seen in all three layers of the arterial wall [136, 140]. PAH develops in the setting of pulmonary arteriole intimal damage, which in turn leads to smooth muscle hypertrophy and fibroblast activation.

Veno-occlusive disease is one of most significant complications arising post-BMT. Pulmonary veno-occlusive disease (PVOD) is rare in comparison to hepatic veno-occlusive disease (VOD) and is often only diagnosed post-mortem [134]. In hepatic VOD in its severest form, there is often concomitant PVOD. The pathophysiology of PVOD involves post-capillary pulmonary venular obstruction resulting in pulmonary vascular congestion and right ventricular failure. PVOD symptoms typically occur weeks to months post-BMT with progressive dyspnoea being a common early symptom. Symptoms of right heart failure develop as pulmonary hypertension worsens. Cytotoxic chemotherapy and irradiation are considered the most significant risk factors for the endothelial injury that develops in PVOD [134].

Radiographic findings on chest X-ray include pulmonary vascular congestion, Kerley B lines and pleural effusions. Bilateral infiltrates may also occur [141]. C.T chest findings include interlobular septal thickening, dilated central pulmonary arteries, and ground-glass opacification [145].

The classically described features of PVOD are a normal or low pulmonary artery wedge pressure (PAWP) on right heart catheterisation [134]. Severe pulmonary artery hypertension, pulmonary oedema on chest X-ray and normal PAWP are characteristics of PVOD [142, 143]. However, not all patients fulfil the criteria, and lung biopsy is the gold standard for diagnosis [144]. Current therapy is limited; treatment options include vasodilators, defibrotide, and corticosteroids [134]. In severe PVOD, lung transplantation is considered definitive treatment; however, recurrence has been reported, and this would suggest a multifactorial aetiology with environmental factors, genetics, and perhaps systemic endothelial dysfunction plays a role in the development of PVOD [145].

Restrictive Lung Disease/Interstitial Lung Disease

Numerous studies have demonstrated the development of restrictive lung disease in post-BMT patients. The restrictive pattern on pulmonary function testing is either an isolated finding or occurs in the presence of a reduced DL_{CO} [108, 146–150]. These findings are typically seen soon after bone marrow transplantation, then improve and stabilise over 12–24 months; however, lung function does not return to pre-transplant results [108, 147, 149, 151]. In the majority of cases, respiratory symptoms and imaging findings are not associated with the pulmonary function

abnormalities [147, 149, 150, 152]. The proposed mechanisms of injury involve interstitial inflammation and fibrosis resulting from irradiation, chemotherapy, immunological impairment and recurrent respiratory infections with remodelling post-injury leading to partial resolution [109].

In the setting of restrictive lung disease with clinical symptoms post-BMT, it is often difficult to determine aetiology and interstitial lung disease; infectious pneumonitis and cryptogenic organising pneumonia (COP) all need to be considered. Alkylating agents, cyclophosphamide, methotrexate and busulfan are all known to be risk factors for developing pulmonary fibrosis. Treatment with steroid may affect an improvement in clinical symptoms; however, a thorough diagnostic workup, including excluding infectious pathology, is advised [112].

In COP (previously known as BOOP) histology reveals patchy areas of consolidation and plugs of granulation tissue in the respiratory bronchioles and alveolar ducts causing chronic interstitial inflammation [124]. COP is associated with both acute and chronic GVHD. Chest radiography typically shows patchy infiltrates, and pulmonary function testing is consistent with a restrictive pattern [153]. COP often improves with corticosteroid therapy; however, the exclusion of infectious pathology is important and may necessitate bronchoscopy and alveolar lavage and in some cases lung biopsy [112].

Long-Term Pulmonary Follow-Up Recommendations

Long-term follow-up protocols are an essential component of survivorship care as a greater proportion of childhood cancer patients progress through adult life and physiological pulmonary decline.

The Children's Oncology Group long-term follow-up guidelines (2013) recommend pulmonary function testing (including spirometry and DL_{CO}) at least once and 2 years post-therapy, in children treated with bleomycin, nitrosoureas, thoracic surgery, and chest radiation.

For paediatric BMT survivors, ongoing follow-up with routine pulmonary function testing (spirometry, plethysmography, and DL_{CO}) is recommended. National Cancer Institute recommendations include pulmonary function testing post-paediatric allogeneic BMT, six monthly for the first 2 years post-transplant then yearly [154]. The role of newer respiratory function tests such as multiple-breath washout and forced oscillation technique is also being evaluated in both paediatric and adult post-BMT populations [155, 156].

While the long-term outcomes of subclinical abnormalities in pulmonary function testing are not yet known, this will be an important clinical issue for patients into adulthood. Long-term sequelae of other known pulmonary insults such as respiratory infections and potential prophylactic and therapeutic interventions remain critical areas for future research.

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