A Clinical Approach to Respiratory Disease in Patients with Haematological Malignancy, with a focus on Respiratory Infection

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Abstract

Respiratory complications, in particular infections, are common in the setting of haematological malignancy and after haematopoetic stem cell transplant. The symptoms can be non-specific and therefore it can be difficult to identify and treat the cause. However, an understanding of the specific immune defect, clinical parameters such as speed of onset, and radiological findings, allows the logical diagnostic and treatment plan to be made. Radiological findings can include consolidation, nodules, and diffuse changes such as ground glass and tree-in-bud changes.

Common infections that induce these symptoms include bacterial pneumonia, invasive fungal disease, Pneumocystis jirovecii and respiratory viruses. These infections must be differentiated from inflammatory complications that often require immune suppressive treatment. The diagnosis can be refined with the aid of investigations such as bronchoscopy, CT guided lung biopsy, culture, and serological tests.

This article gives a schema to approach patients with respiratory symptoms in this patient group, however in the common scenario of a rapidly deteriorating patient, treatment often has to begin empirically, with the aim to de-escalate treatment subsequently after targeted investigations.

Introduction

Haematological malignancy is relatively common, with a prevalence of 549 per 100,000 and approximately 328,000 cases in the UK [1] at any one time. They consist of a heterogenous group of diseases that are treated with high dose chemotherapy, often followed by haematopoetic stem cell transplant (HSCT).

The diseases themselves as well as the treatments lead to significant immunosuppression, leaving the patients susceptible to infections that often affect the respiratory system. As a consequence, approximately 50% of patients with a haematological malignancy develop respiratory infections during the course of their treatment [2]. Although this article focuses on the infective complications of haematological malignancy, non-infectious disorders account for approximately half of respiratory complications post HSCT [3], and must always be actively considered in the differential diagnosis. Table 1 shows some of the more common and serious non-infectious problems that arise post HSCT. As treatment for non-infectious disorders often requires increased immunosuppression, significant infection usually has to be excluded prior to commencing treatment for a non-infectious pulmonary complication of haematological disease.

Sources of Infecting Organisms

Organisms causing infections reach the lung from a variety of sources. These pathogens include both common gram positive and negative pathogens such as respectively *Staphylococcus aureus* and *Pseudomonas aeruginosa,* as well as anaerobes (see table 2) [4]. Many bacterial pathogens are nasopharyngeal commensals, which immunosuppressed individuals are less able to effectively clear from the lungs after aspiration. Respiratory pathogens are also commonly inhaled from infected contacts by droplet spread. The commonest causative organisms in this group are the respiratory viruses (see table 3), which usually only cause mild, self-limiting infections in immunocompetent individuals but in patients with haematological malignancy present with relatively severe symptoms, prolonged infection, and higher rates of pneumonia and death [5–7]. Less common causes of inhaled droplet lung infections are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Mycobacterium tuberculosis* (table 3). Inhalation of environmental organisms that do not usually cause infection in an immunocompetent host is another significant source of respiratory infection. These include *Aspergillus* species, other filamentous fungi, *Nocardia*, and non-tuberculous mycobacteria. *Aspergillus* in particular can affect up to 10% of patients with haematological malignancy [8]. Immunosuppression associated with haematological malignancy may also allow reactivation of organisms that are either dormant or persist at low numbers within the lung. These pathogens include *Pneumocystis jirovecii* which seems to be a lung commensal that replicates to cause disease in certain types of immunosuppression unless patients are given appropriate prophylaxis [9]. Reactivation is also the mode of infection for pneumonitis caused by cytomegalovirus (CMV) and other herpes

viruses, and for some cases of *M. tuberculosis* occurring in subjects with latent infection. Finally infections from other parts of the body can spread to the lung via haematogenous spread, for example *Candida* species and bacterial seeding as septic emboli from indwelling catheters and lines.

Clinical Approach

The multiple potential infecting organisms, with a corresponding variety in antimicrobial treatment options, can make selection of the appropriate management strategy difficult. Fortunately an understanding of the specific immune deficiencies that act as specific risk factors for specific organisms (table 4) in combination with clinical parameters such as speed of onset (table 5) and radiological appearance usually allows the differential diagnosis to be narrowed down. This in turn then allows the formation of a logical targeted diagnostic and treatment plan. In patients who do not improve rapidly with first line therapy with broad spectrum antibiotics, cross-sectional thoracic CT imaging is essential as it provides much better definition of the pattern of radiological changes than a chest radiograph. These radiological patterns can be broken down into 3 main groups: consolidation, nodules (micro- and macro-), and diffuse changes, which can be further sub-divided into ground glass and tree-in-bud patterns. We discuss the likely causes for each of these radiological patterns and how this guides the appropriate initial investigations and treatment options.

Consolidation

Dense focal consolidation (figure 1A) often develops rapidly in the context of fevers, dyspnoea and elevated C-reactive protein (CRP). This clinical pattern is highly suggestive of pneumonia caused by pyogenic bacterial pathogens [10] associated with community and hospital acquired pneumonias, often originating from microaspiration of nasopharyngeal commensals. Blood and sputum cultures are essential, and treatment with broad-spectrum antibiotics incorporating gram negative cover should be commenced, and most patients will respond to these making invasive investigation with bronchoscopy unnecessary. However, if the patient does not respond rapidly, i.e. within 48 to 72 hours, infection with a highly resistant organism such as methicillin resistant *S. aureus* or multi-resistant *P. aeruginosa* (resistant to 3 of the following: carbapenem, ceftazidime, tobramycin, or ciprofloxacin) should be considered. This will necessitate escalation to second-line antibiotics and if the patient can tolerate bronchoscopy, bronchoalveolar lavage (BAL) of the affected lobe should be performed to try and obtain a clear microbiological diagnosis.

Focal consolidation with a sub-acute onset has a broader differential diagnosis; these include bacterial pneumonia, *Aspergillus* species and *Nocardia* species (usually *asteroides*), and non-infectious causes such as organising pneumonia and recurrence of haematological malignancy. Diagnostic tests including BAL for culture, galactomannan [11], and cytology are necessary. While transbronchial biopsy has low yield and is not recommended for the diagnosis of invasive fungal disease [12] given the complication rate of pneumothorax in particular, it may be useful in confirming alternative diagnoses. Dense peripheral lesions adjacent to the pleura are amenable to CT guided percutaneous biopsy. Histology can rapidy confirm a diagnosis of invasive fungal disease (IFD), *Nocardia* infection,

organising pneumonia, or malignant infiltrations (e.g. lymphoma), and the biopsy materal can also be sent for culture.

Pulmonary Nodules

Pulmonary nodules are rounded lesions within the lung with a diameter greater than 4mm in diameter, but in the haematological malignancy population they are often substantially larger than this and can be termed macronodules. The presence of macronodules should always raise the suspicion of an IFD, the commonest of which is invasive aspergillosis, the majority of which are caused by *A. fumigatus*. Several other *Aspergillus* and filamentous fungi species such as mucormycetes can cause IFD and have similar clinical and radiological findings [8]. The CT scan has several distinct appearances that increase the likelihood that a macronodule is caused by IFD, though are not necessarily very specific. A surrounding halo of ground glass (figure 1B) is a classical sign of angioinvasive fungal disease, with the halo representing haemorrhage, and the air crescent sign (figure 1C) due to the formation of a fungal ball within a cavity caused by fungal destruction of lung tissue is also highly suggestive of IFD [13,14]. Macronodules caused by IFD undergo a classic evolution of changes on CT as the infection is controlled, with the nodule developing the air crescent sign, followed by thinning of the cavity wall and shrinkage of its overall size, associated with clearance of the associated surrounding consolidation [15].

A recently described CT sign that points to IFD is the occluded vessel sign [16], where pulmonary arteries are interrupted within areas of consolidation. This had a 89% sensitivity and 52% specificity for proven or probable IFD by EORTC

148 criteria [17], but does require a CT pulmonary angiogram protocol with contrast
149 injection, with its attendant risks of renal toxicity and allergic reactions.
150 Similarly the hypodense sign, central hypoattenuation within a macronodule, has
151 recently been shown to have a similar sensitivity (46%) and superior specificity
152 (83%) to the halo sign for IFD [16,18]. The reverse halo (also termed the atoll sign)
153 is a strong indicator for mucormycosis early in the disease course of neutropenic
154 patients [19].

155 Although CT appearances of macronodules can be highly suggestive of IFD,
156 microbiological confirmation gives additional confidence in the diagnosis and
157 ensures the patient receives antifungal treatment that is effective against the
158 specific infecting fungal pathogen. Unfortunately, all existing microbiological
159 tests for IFD have significant drawbacks. Culture of BAL [20,21] or sputa is
160 insensitive [22] although when positive in the immunosuppressed patient is highly
161 suggestive of active infection. Antigen testing using the serum galactomannan
162 has a sensitivity of 41-78% and specificity of 60-95% when two sequential
163 samples have an optical density >0.5 giving a negative predictive value of up to
164 95% in azole naïve patients in the highest risk groups (neutropenic patients)
165 [15,23,24], but does not confirm IFD species. Furthermore, serum galactomannan is
166 less accurate in patients receiving triazole prophylaxis [24–26], which is now in
167 widespread use in haemato-oncology patients. Measuring galactomannan in BAL
168 instead has a much greater sensitivity of 87% and specificity of 89% even in the
169 setting of triazole prophylaxis [24], and hence a negative BAL galactomannan can
170 allow de-escalation of treatment with antifungals. Mucormycetes have little
171 galactomannan in their cell walls rendering serum and BAL analysis for this test
172 insensitive [27]. *Aspergillus* PCR should be sensitive but may not be specific due to

widespread presence of *Aspergillus* species in the environment, and as yet there is little standardisation between kits and is not in widespread use [28]. The lateral flow device provides a point of care test for fungal wall antigens that is as sensitive and specific as PCR [29] and has significant clinical promise but is not yet in wide commercial use.

As discussed above in the consolidation section, a CT guided percutaneous biopsy is a rapid way of identifying IFD in macronodules, as well as some other pathogens, and non-infective diagnoses. The biopsy material can also be sent for culture to identify the infecting species and antimicrobial resistance profile. Haemorrhage and pneumothorax are the main complications of percutaneous CT guided biopsies, with the former being a particular problem in haematological malignancy due to the prevalence of significant thrombocytopenia. However, targeting peripheral lesions and using platelet transfusions minimises these risks.

Overall, a specific diagnosis of invasive fungal disease can be difficult to achieve and microbiological diagnosis of IFD remains unreliable. Diagnosis is usually made with a consideration of multiple elements: clinical risk factors, radiological changes, biomarkers, and the use of triazole prophylaxis. As mortality without treatment is high [30,31], empirical treatment is usually started in high-risk patients as soon as the clinical picture is compatible with an IFD. Although published data suggests that azoles such as voriconazole and posaconazole are as effective as amphotericin (if not moreso) [15,32], liposomal amphotericin is often the first line therapy in patients receiving azole prophylaxis due to fears about fungal resistance [33,34]. If azoles are used, ensuring that therapeutic levels are achieved

by monitoring serum levels improves outcomes [35–38]. Newer azoles are being developed, and one of these isavuconazole has recently been shown to be non-inferior to voriconazole and has the advantage of being effective against mucormycosis [39]. Dual agent antifungal may have superior outcomes in IFD, and could be considered in critically ill patients [40,41].

Other causes of nodules include septic emboli, *Nocardia*, mycobacterial infections, and non-infectious causes. Septic bacterial emboli cause distinctive radiological appearances of multiple cavitating nodules, usually in the lung periphery and often eroding into the pleural space to cause infected hydropneumothoraces. The most common sources are infected indwelling catheters, so line infection needs considering in any patient with radiological evidence of lung nodules, necessitating paired blood and line cultures. Multiple well-defined micronodules in the context of cell mediated immune deficiency can be caused by *Nocardia* [42] and mycobacterial species [43]. Nocardial infection is associated with myeloablative conditioning and steroids, with a median time to infection of 10 months post HSCT [42]. Pulmonary infection has a mortality rate up to 53% and requires treatment for 6 to 12 months with oral trimethoprim/sulphamethoxazole or parenteral treatment with carbapenems and/or amikacin. Prophylactic trimethoprim/sulphamethoxazole for pneumocystis also protects against *Nocardia*. Non-tuberculous mycobacteria infection post HSCT has an incidence of between 0.4 and 10% [44], associated with GvHD and further immunosuppression, and has a 7-19% mortality rate [45,46].

Non-infectious causes of nodules such as lymphoma, other malignancies, and post transplant lymphoproliferative disorder (PTLD) need histological diagnosis.

However, smaller size nodules may not be amenable to percutaneous biopsy, the yield of BAL remains poor, and in the non-responding patient the diagnosis may require video assisted thoracoscopic biopsy. In these situations it is important to try and identify potential extrathoracic sites of disease that are more amenable to biopsy than the lung.

Diffuse Disease

The differential diagnosis for diffuse, less dense, bilateral infiltrations on the CT scan is broad. These changes encompass two main patterns, ground glass infiltrates and tree-in-bud changes, which differ in their likely causes and are discussed separately below. The important microbiological tests are blood and sputum cultures, serum β-D-glucan antigen testing (a fungal cell wall component), blood CMV viral load, and multiplex PCR for respiratory viruses on nasopharyngeal aspirate. Inflammatory markers such as CRP can help differentiate between infectious and non-infectious causes, although CRP can also be significantly elevated in non-infective hyperinflammatory states. Serial full blood counts and coagulation status can help identify patients at risk of engraftment syndrome (clinical syndrome occurring at time of neutrophil recovery) or pulmonary haemorrhage. Obtaining BAL for cytology and microbiological testing is very helpful, but these patients are often too hypoxic to undergo a bronchoscopy.

Ground glass infiltrates

Bilateral ground glass infiltrates (figure 1D) can be caused by a wide range of microbial pathogens including pyogenic bacteria, respiratory viruses, cytomegalovirus, *Pneumocystis jirovecii*, and multiple non-infective causes. This pattern is unlikely to be caused by an IFD. Often ground glass infiltrations are associated with areas of denser consolidation creating a mixed appearance on the CT scan. The likely causes of rapid onset of bilateral ground glass infiltrates over a few days include bacterial infections, pulmonary oedema, and ARDS, and less commonly alveolar haemorrhage or engraftment syndrome. Engraftment syndrome presents with widespread infiltrates associated with fever, rash, and other organ dysfunction within 4 days of granulocyte recovery post-HSCT [47]. A sub-acute onset of respiratory symptoms over days and weeks with associated ground glass changes has similar causes as acute presentations, but the differential diagnosis needs to be expanded to include *P. jirovecii*, CMV, respiratory viruses, and drug- or radiotherapy-induced pneumonitis. There are some aspects of the clinical presentations of the above diseases that can suggest the underlying cause, and these are discussed below.

Pneumocystis pneumonia (PJP, previously referred to as PCP in older publications) often has a distinct clinical presentation of progressive dyspnoea over several weeks associated with desaturation on exertion and then eventually hypoxaemia. This is usually associated with only low-grade fevers and moderate increases in CRP. The incidence is as low as 0.1% in patients receiving prophylaxis [48]. Pulmonary co-infection is common, particularly with CMV, and mortality rates have been reported to be as high as 30-60% in haematological malignancy [49], though in our experience it is considerably less than this. CT findings are often highly suggestive of PJP, classically showing diffuse bilateral

ground glass shadowing with a predilection for the upper lobes and marked subpleural sparing. Serum antigen testing for β-D-glucan is very helpful, with a published sensitivity of 95% and specificity of 86% for PJP [50,51]. However, β-D-glucan levels can also be elevated with other fungi, in particular with candidaemia, so need to be interpreted in the context of the overall clinical picture. The diagnosis of PJP can also be confirmed in some patients by identification of cysts in bronchoalveolar lavage using immunofluorescence, although this is often negative in haematology patients. Overall, in patients with a classical clinical and radiological presentation the diagnosis of PJP can be confirmed by the response to empirical treatment, usually with high dose co-trimoxazole or clindamycin and primaquine. Adjunct systemic corticosteroids are used in hypoxic patients, but do complicate assessing the response to empirical treatment as non-infective causes of a pneumonitis can also improve with corticosteroid treatment.

CMV pneumonitis is most often due to reactivation of latent infection during periods of impaired cell mediated immunity and T cell depletion rather than primary infection, and has a high mortality of up to 50% [52]. CT findings in CMV pneumonia are not that distinctive, and include bilateral ground glass infiltrates and symmetrical micronodules [53]. The diagnosis is suggested by highly elevated blood CMV viral load, especially if this has increased rapidly, and can be confirmed by obtaining BAL fluid for quantitative PCR [54] and cytology to look for viral inclusion bodies. However, the patients are often too hypoxic for a safe bronchoscopy. Treatment is with intravenous ganciclovir, followed by conversion to valganciclovir, with foscarnet and cidofovir as second and third line agents [55].

Although there can be clinical (for example, rapid weight gain suggesting fluid retention and pulmonary oedema), and radiological features (Table 1) that suggest specific causes, making a confirmed diagnosis of non-infective aetiologies of bilateral infiltrates is often difficult. The diagnosis often partially depends on microbiological testing to try and exclude infective causes, including bronchoscopy if the patient is able to tolerate the procedure. Bronchoscopy can also be diagnostic for alveolar haemorrhage with similar or increasing recovery of bloody fluid with sequential lavage. The main clinical decision is whether to introduce systemic corticosteroids as a treatment for suspected non-infective causes such as drug- or radiation-pneumonitis, alveolar haemorrhage, or rarer complications of specific therapies such as all-trans retinoic acid differentiation syndrome.

Tree-in-bud changes

Bilateral tree-in-bud (figure 1E) changes are suggestive of acute respiratory viral infections (Table 3) or widespread bacterial bronchiolitis. This can sometimes be seen in patients with bronchiectasis as a complication of haematological disease (for example, secondary to hypogammaglobulinaemia). Respiratory viral infections are very common in patients with haematological disease, and can now be readily diagnosed by PCR on a nasopharyngeal aspirate. The CT often demonstrates widespread, diffuse, symmetrical tree-in-bud changes although these infections can also cause ground glass infiltrates. In comparison to immunocompetent individuals, respiratory viral infections in patients with haematological malignancy (particularly after HSCT) are more prolonged, lasting

weeks and even months, and lead to an increased risk of respiratory compromise due to the development of viral or secondary bacterial pneumonia [56]. The viruses recognised to cause respiratory infection in haemato-oncology patients are noted in table 3. Some have specific treatments though the data for efficacy are largely limited to case series. Ribavirin is used for respiratory syncytial virus (RSV), though appears to have little effect once patients develop respiratory failure [57]. Adenovirus is often cultured, though less commonly causing infection, can be treated with Cidofovir [58,59]. Neuraminidase inhibitors reduce mortality due to influenza infection [60], though are less effective in patients who are immunosuppressed, have GvHD, lymphopenia or older age [61]; pre-emptive vaccination is key in preventing infection [62]. There are no recognised organism-specific treatments for parainfluenza [63], human metapneumovirus [7], and rhinovirus [64].

Bronchiectasis is a common complication of many haematological diseases including multiple myeloma, chronic lymphocytic leukaemia (CLL), B cell depletion therapies, and HSCT, and can result in subacute bacterial bronchial infections. These cause patchy tree-in-bud infiltrates associated with bronchial wall thickening and dilatation, and are usually caused by Gram negative pathogens such as *K. pneumoniae* or *P. aeruginosa* that will require prolonged therapy with appropriate antibiotics. Too short an antibiotic course will allow the infection to recur and this can lead to a vicious cycle of recurrent infections with an inability to gain weight or fully recover before the next infection occurs. Antibiotic prophylaxis and correction of hypogammaglobulinaemia with supplementary immunoglobulins is important for these patients, and is also

recommended in other patients with haematological malignancy and secondary antibody deficiency in the setting of recurrent infections [65].

Treatment Strategies

Almost all haematology patients presenting acutely with fever and dyspnoea will require broad-spectrum antibiotics. Starting antifungals with the initial fever does not improve outcomes compared to delaying to day 4 if the fever does not settle [66]. Similarly, cross-sectional CT is only necessary if the symptoms do not resolve rapidly with antibiotics [67]. If the fever persists, then characteristic CT changes in the clinical context (speed of onset, immune defects, other clinical features) will often indicate the need for specific treatments, e.g. liposomal amphotericin or voriconazole in neutropenic patients with a macronodule with surrounding halo. However, the wide differential diagnosis means that empirical treatment targeting different infectious and non-infectious causes is often required. Microbiological confirmation remains variably successful; culture techniques are slow and sensitivity can be poor, hence the development of biomarkers and PCR to increase sensitivity. While invasive procedures such as bronchoscopy or biopsy can give vital diagnostic information and in particular allow the de-escalation of antifungals and make alterntive diagnoses, patients can deteriorate rapidly and be too hypoxic for such investigations.. Furthermore, many cases of respiratory problems in haematology patients have a combination of causes so even when a microbe has been identified this may not prevent broader treatment. Another significant issue is when to stop therapy in patients treated empirically with multiple agents who then improve, as the cause of the

underlying problem may remain unclear. Most bacterial infections resolve with a few days of antibiotics, but aspergillosis can require prolonged therapy to prevent recurrence. Exactly how long antifungals should be continued is not known; serum galactomannan levels may have some utility, with a ≥35% reduction after 1 week associated with a good clinical outcome [68,69], but mainly outcome is monitored by observing radiological responses. It is unclear at which stage during this evolution that it is safe to stop antifungals without leading to a significant risk of recurrence.

Conclusion

Patients with haematological malignancy can develop a range of immune defects during the course of their illness or associated with the necessary treatments. These allow various pathogens to cause disease, and the respiratory tract is commonly affected; this is associated with significant morbidity and mortality. Infections must be treated promptly, requiring empirical therapy chosen to cover the most likely pathogens given the clinical presentation. An understanding of the relevant immune defect along with the recognition of patterns of clinical presentation and findings on cross-sectional CT imaging, allows logical deduction of likely culprits and targeted microbiological and molecular investigations to help narrow the differential diagnosis. This is with the caveat that there is significant cross-over between radiological findings, and a high prevalence of non-infective respiratory complications that are often diagnoses of exclusion. As such there are many occasions when the specific diagnosis is never discovered and critically ill patients have to be treated for

multiple organisms and non-infective complications empirically. There is an urgent need for improved rapid diagnostics with better sensitivity and specificity to allow more directed treatment of respiratory infections in haematological malignancy. Ideally future research should focus on the development of point of care tests that accurately identify specific organisms. If possible these will be non-invasive and easy to perform even on critically ill patients, allowing pathogen-specific treatments and minimising unnecessary drug-related toxicity.

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Table 1: Acute and sub-acute non-infectious respiratory complications in the immunosuppressed patient

Clinical problem	Common radiological features
Acute presentation (hours to days)	
Pulmonary oedema	Cardiomegaly, upper lobe diversion, interstitial oedema and pleural effusions
Acute respiratory distress syndrome (ARDS)	Bilateral ground glass, dependent consolidation, traction bronchiectasis
Diffuse alveolar haemorrhage	Rapidly progressive ground glass changes
Engraftment syndrome	Interstitial oedema and pleural effusions
Thoracic air leak syndrome	Pneumothorax, pneumomediastinum, subcutaneous emphysema
Leukostasis	Interstitial infiltrates and/or alveolar opacification
Sub-acute presentation (days to weeks)	
Idiopathic pneumonia syndrome	Diffuse bilateral infiltrates
Organising pneumonia	Peribronchial and peripheral air space opacification
Radiation pneumonitis	Ground glass and consolidation within the radiation field developing into pulmonary fibrosis
Drug toxicity	Bilateral alveolitis (ground glass infiltrates), developing into pulmonary fibrosis
Chronic presentations (weeks to months)	
Pulmonary veno-occlusive disease	Enlarged pulmonary arteries, smooth interlobular septal thickening, ground glass opacities
Lung graft versus host disease (GvHD)	Mosaicism, progressive airway dilatation
Post transplant lymphoproliferative disorder (PTLD)	Pulmonary nodules and mediastinal lymphadenopathy
Pleuroparenchymal fibroelastosis	Fibrotic thickening of pleura and subpleural parenchyma
Non-classifiable interstitial pneumonia (pulmonary fibrosis)	Ground glass, peribronchial crazy paving, reticulation and traction-bronchiectasis

661 **Table 2:** Bacteria that cause respiratory infection in patients with haematological
662 malignancy (modified from [4])

Gram positive	Gram negative	Anaerobes	Atypical
Streptococcus pneumoniae	*Pseudomonas* spp.	*Prevotella* spp.	*Mycoplasma pneumoniae*
Streptococcus pyogenes	*Klebsiella pneumoniae*	*Fusobacterium* spp.	*Chlamydophila pneumoniae*
Staphylococcus aureus	*Escherichia coli*	*Bacteroides* spp.	*Legionella* spp.
Nocardia asteroides	*Enterobacter cloacae*		
Rhodococcus equi	*Stenotrophomonas maltophilia*		
	Citrobacter spp.		
	Serratia marcescens		
	Acinetobacter baumanii		
	Haemophilus influenzae		
	Proteus spp.		
	Burkholderia spp.		
	Achromobacter spp.		
	Moraxella catarrhalis		

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665 **Table 3:** Fungi, viruses, and mycobacteria that cause respiratory infection in patients
666 with haematological malignancy (modified from [4,43])
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Fungi	Viruses	Mycobacteria
Candida spp.	Respiratory viruses:	*Mycobacterium tuberculosis*
Aspergillus spp.	Influenza A and B	
Other filamentous fungi:	Parainfluenza 1-3	Non-tuberculous mycobacteria:
Fusarium spp.	Human metapneumovirus	*Mycobacterium avium-intracellulare complex*
Scedosporium spp.	Adenovirus	*Mycobacterium abscessus*
Mucor spp.	Coronavirus	*Mycobacterium fortuitum*
Rhizopus spp.	Respiratory syncytial virus	*Mycobacterium kansasii*
Pneumocystis jirovecii	Rhinovirus	*Mycobacterium chelonae*
Environmental fungi:	Herpesviruses:	
Histoplasmosis	Cytomegalovirus	
Coccidiomycosis	Varicella zoster	
Cryptococcus neoformans	Herpes simplex	
	Human herpes virus 6	

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670 **Table 4:** Common infective causes of respiratory symptoms in patients with
671 haematology malignancy categorised by immune defect
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Immune defect and common associations	**Common pathogens**
Neutropenia / functional neutrophil defects: Leukaemia Aplastic anaemia / bone marrow infiltrations HSCT Chemotherapy	Bacterial pneumonia *Aspergillus* spp. Other filamentous fungi Invasive candidiasis
Impaired T cell function HSCT Immunosuppressive therapies Lymphoma	*P. jirovecii* Respiratory viruses Cytomegalovirus Other herpesviruses Mycobacteria Nocardia
Immunoglobulin deficiency (mainly IgG) CLL Myeloma HSCT B cell depletion therapies	Bacterial pneumonia Bacterial exacerbations of bronchiectasis Respiratory viruses
Prolonged high dose corticosteroids	*P. jirovecii* *Aspergillus spp.* Respiratory viruses Cytomegalovirus Mycobacteria Bacterial pneumonia
Kinase inhibitors JAK inhibitors (e.g. Ruxolitinib) BCR pathway inhibitors (e.g. Ibrutinib)	 *Aspergillus spp.* *P. jirovecii* Bacterial pneumonia *Aspergillus spp*. *P. jirovecii*

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Table 5: Causes of respiratory symptoms in haematological malignancy categorised by speed of onset

Speed of onset	Infective causes	Non-infective causes*
1-3 days	Bacterial pneumonia	Pulmonary oedema Diffuse Alveolar Haemorrhage Adult respiratory distress syndrome Engraftment syndrome
3-7 days	Bacterial pneumonia Respiratory viruses *M. pneumoniae*	Adult respiratory distress syndrome Engraftment syndrome
1-2 weeks	Respiratory viruses *M. pneumoniae* CMV / other herpesviruses	Drug / radiation pneumonitis Idiopathic pneumonitis
2-6 weeks	*Aspergillus* spp. Other filamentous fungi *Nocardia* spp. *M. tuberculosis* *Pneumocystis jirovecii*	Drug / radiation pneumonitis Idiopathic pneumonitis Lung GvHD Organising pneumonia Lymphoma / malignant infiltration PTLD
Months	*M. tuberculosis* Non Tuberculous Mycobacteria	Lymphoma / malignant infiltration Drug / radiation pneumonitis (fibrotic phase) Bronchiectasis Organising pneumonia PTLD Lung GvHD Post-allograft restrictive lung disease / Pleuroparenchymal fibroelastosis

*pulmonary emboli can present in any time category

683 Figure Legend
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685 Figure 1. Cross-sectional radiological images in respiratory complications of
686 haematological disease. A) Consolidation due to bacterial pneumonia, B) Halo
687 with surrounding ground glass in invasive mould disease, C) Air crescent sign
688 (white arrowhead demonstrates crescent) in partially treated invasive mould
689 disease after neutrophil recovery, D) Ground glass changes due to *P. jirovecii,* E)
690 Tree in bud changes due to respiratory viral infection, F) Atoll/reverse halo sign
691 due to organising pneumonia.