

Pro/con debate

Pro: Bronchoscopy is essential for pulmonary infections in patients with haematological malignancies

Up to 60% of patients with haematological malignancy will develop pulmonary infiltrates at some point in their disease course. Bronchoscopy should be used early in patients without respiratory failure as diagnostic yield is highest in the first 1–2 days of illness. Perceptions that patients with haematological malignancy are at higher risk of complications from bronchoscopy has led to a reluctance to perform the procedure. However, cohort studies have not demonstrated any increase in complications for this specific patient group. Common concerns include mucosal injury, respiratory impairment and haemorrhage. However, prospective cohort studies demonstrate that this patient group do not experience a higher than baseline level of complications. Specific pathogen diagnosis reduces morbidity and mortality in lung infection. Additionally, complex infections with multidrug-resistant organisms, the increasing prevalence of which is largely driven by empirical antibiotic use, make specific diagnosis more crucial than ever if we are to maintain our ability to manage myelosuppressive therapies and stem cell transplant.

Up to 60% of patients with haematological malignancy will develop pulmonary infiltrates at some point in their disease course [1, 2]. Infectious complications have now surpassed tumour resistance to chemotherapy as the major obstacle to patient survival. Early specific pathogen diagnosis is paramount for mortality reduction. The lungs are the most common site of neutropenic infection and the risk of opportunistic infection is increased by direct pulmonary toxicity from chemotherapy and

graft *versus* host disease (GVHD) [1–4]. The litany of potential lung insults includes: aspiration risk from treatment-associated mucositis, viral pneumonitis and other infectious pneumonia, GVHD, cardiogenic pulmonary oedema, pulmonary embolism, leukaemic infiltration or direct chemotherapy-induced lung toxicity. This wide range of potential mechanisms creates broad differential diagnoses for pulmonary infiltrates [4]. Bronchoscopy should be used early in patients without respiratory failure. Early bronchoscopy increases the diagnostic yield and avoids the patient later becoming too unwell for the procedure [1–4]. Diagnostic yield falls with duration of patient exposure to empirical antimicrobials. Bronchoscopies performed within 1–2 days of symptom onset have the highest success rate in excess of 50% in neutropenic and 60% in non-neutropenic patients for identifying causative pathogen [2–5]. Bronchoscopy is also advisable for patients with focal opacities that are not quickly responding to empirical regimens [5].

Recent advances in molecular diagnostics raise questions about the ongoing need for invasive testing; however, invasive sampling remains an essential diagnostic tool and newer molecular assays have actually increased the yield of bronchoscopic sampling rather than removing the need for it. Impaired sputum production is also often a barrier to the accuracy of noninvasive testing [3]. Perceptions that patients with haematological malignancy are at higher risk of complications from bronchoscopy has led to a reluctance to perform the procedure. However, cohort studies have not

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demonstrated any increase in complications for this specific patient group [6–8]. Complex infections with multidrug-resistant organisms (MDRO), the increasing prevalence of which is largely driven by empirical antibiotic use, make specific diagnosis more crucial than ever. Bronchoscopy will continue to be an important diagnostic tool to evaluate pulmonary infiltrates in haematological malignancy patients for the foreseeable future. The diagnostic yield of bronchoscopy is variable depending on the population studied, the assays requested and the timing of the procedure in the disease course.

Complications: bronchoscopy is far less risky than many clinicians think

Reluctance to perform bronchoscopy on oncohaematological patients is in large part related to the perception that this group is at higher risk of procedural complications. Common concerns include mucosal injury, respiratory impairment and haemorrhage. However, prospective cohort studies demonstrate that this patient group do not experience a higher than baseline level of complications [3, 6–9]. A 1995 study recorded only two minor self-limiting bronchial haemorrhages in 246 total procedures [3]. Cohort studies in the past 5 years demonstrated no complications at all, either respiratory or vascular [7–10]. A large prospective randomised control trial of bronchoscopy in intensive care patients either with solid organ or haematological malignancy noted no increase in the complication rate in the haematological malignancy subgroup when compared with the other patients [6]. Although concern regarding increased morbidity and mortality is understandable, there is no convincing evidence for increased procedural complications in haematology patients. Modern molecular techniques have increased diagnostic successes and more recent studies that include PCR and pathogen-specific assays in addition to traditional Gram-stain and culture demonstrate higher rates of pathogen identification [7–9]. Current recommendations are that BAL and brushing samples should be sent for immunofluorescence studies, Gram-stain and culture, immunofluorescence for cytomegalovirus (CMV) and multiplex PCR. Cytological examination should be performed for viral inclusion bodies. Tests for malignant and other disease related processes can be performed simultaneously [7–9, 11].

Bronchoscopy has superior sensitivity and specificity compared with noninvasive modalities

Where available, bronchoscopy offers superior specificity and sensitivity in comparison to

noninvasive modalities. Chest computed tomography (CT) is highly sensitive for pulmonary abnormalities, but the findings are general, nonspecific and may appear late in the disease course with immunosuppression [12–14]. High-resolution CT (HRCT) of the lung is superior to non-high-resolution imaging, but sensitivity and specificity values vary dependent on post-transplantation phase (*i.e.* neutropenic, first 100 days, or beyond 12 months) and disease process [10, 15]. Regardless, CT should be obtained initially and can be used to identify optimal sample site for invasive testing as well as in cases where collection of tissue or sputum for culture is not possible [11, 15, 16]. The yield of induced sputum samples is higher than routine sputum samples only for mycobacteria, *Pneumocystis jirovecii* and cytology [9, 13]. Selected blood assays can also be useful, but generally have lower sensitivity and specificity than targeted lower respiratory tract samples. Some blood assays, such as quantitative CMV PCR or galactomannan, may be suggestive of specific conditions but tissue biopsy is necessary to confirm organ involvement. Fungal pneumonia requires tissue confirmation for diagnosis, and is common, with the estimated incidence in the neutropenic phase following stem cell transplant (SCT) being from 12% to 45% [1]. Serological testing in general is unreliable in immunosuppression as it may be falsely negative [14, 17]. CT-guided lung biopsy carries a higher risk of complications than bronchoscopy, including acute pneumothorax and has not been widely studied in neutropenic patients; however, it is recommended in patients with lesions not anatomically amenable to transbronchial biopsy [15, 18, 19].

Getting the diagnosis right early avoids unnecessary and potentially toxic empiric anti-infective therapy, and is associated with decreased mortality

Correct and early diagnosis of causative pathogens has been shown to reduce morbidity and mortality in patients with haematological malignancy and pulmonary infection [11, 19]. Factors contributing to improved outcomes include: timely administration of a targeted antimicrobial agent, reduced adverse effects of broad empirical antibiotic regimens, identification of atypical pathogens, and prevention of MDRO acquisition with less broad-spectrum empirical regimen exposure. Without a pathogen-based diagnosis, we are just guessing. In fact, “adequate” empirical therapy for all likely pulmonary pathogens post-SCT would probably require meropenem, vancomycin, liposomal amphotericin B, ganciclovir and cotrimoxazole. This regimen is

dangerous and expensive with potentially catastrophic side-effects and drug interactions.

Many conditions require specific diagnosis for good clinical outcome. In *Pneumocystis jirovecii* pneumonia (PJP) induced sputum microscopy has low sensitivity in non-AIDS patients, ~50% compared to 97% in bronchoalveolar lavage (BAL). Beta-D-glucan assay on peripheral blood is nonspecific and can be elevated in other forms of fungal infection and *Pseudomonas* pneumonia as well as PJP [13]. Lower respiratory tract specimens for testing are thus recommended whenever PJP is suspected. This can be achieved with induced sputum; however, this is not always available, is an infection control challenge and can induce respiratory distress and deterioration. Empirical cotrimoxazole is an alternative, but has drawbacks due to associated high incidence of acute kidney injury (in a population where renal impairment is common due to cytotoxic exposure) and hyperkalaemia. Aspergillosis is the most common invasive pulmonary fungal disease, but lower airway specimens are again required to differentiate infection from upper airway carriage. Only 30% of cases with invasive aspergillosis will demonstrate classic radiological signs (tree in bud distribution) [10]. BAL galactomannan demonstrated a sensitivity of 91% for diagnosis of invasive aspergillosis, compared with 50% and 53% for culture and microscopy, respectively [9]. Broad-spectrum empirical coverage of fungal disease, including zygomycetes, requires amphotericin B and/or posaconazole, both expensive and potentially toxic options. A high CMV viral load in blood may point towards end-organ disease, but this has very poor specificity and a local tissue sample is required to confirm viral replication at the site. The toxicity of ganciclovir is too much to justify empirical treatment without further diagnostic workup. Furthermore, at least 5% of CMV isolates now demonstrate resistance to at least one antiviral agent, and the treatment for these strains is even more toxic (foscarnet, cidofovir) or expensive (letermovir) [14].

Multidrug-resistant bacteria are increasingly common and must be identified and targeted for successful outcomes

MDRO acquisition (*e.g.* methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and carbapenem-resistant Enterobacteriaceae) is associated with increased morbidity and mortality [4]. The potential for clinical infection with an MDRO in haematology patients exceeds that of the general population due to increased nosocomial contact and prophylactic antimicrobial regimens. In South East Asia,

Europe and North America, ventilator-associated pneumonia caused by multidrug-resistant Gram-negative rods (MDR-GNR) now approaches a prevalence of 70% [18]. MDR-GNRs are classified by the World Health Organization as priority one pathogens of concern due to escalating resistance rates. Empirical antibiotic use (in conjunction with agricultural and targeted antibiotic use) have played a large part in creating this problem.

Antimicrobial resistance is often perceived to be a general threat to public health rather than a specific threat to individual immunosuppressed patients. Exposure to last-line agents as part of empirical regimens can induce resistance in the patient's own individual microbiome. Expression of fluoroquinolone and beta-lactam resistant phenotypes of *Pseudomonas aeruginosa* after only very limited exposure to antibiotics is a common example [20]. Clinicians also often underestimate how quickly pathogens can acquire resistance. The emergence of carbapenemase-producing organisms has not stopped the increasing empirical use of carbapenems, although the link between the two phenomena is clear. If a patient is exposed to unnecessary antibiotics, their risk of MDRO acquisition and potential MDRO clinical infection is increased without benefit to offset the risk. Vigilant antibiotic stewardship will give longevity to our ability to manage the complications of myelosuppression. Bronchoscopy is an important diagnostic tool for ensuring antibiotics are correctly targeted with the narrowest spectrum possible.

Bronchoscopy has a high yield in this population, and frequently leads to a change in anti-infective treatment

Cohort studies show that while bronchoscopy does not have a higher complication rate in oncohaematological patients it frequently leads to pathogen identification and subsequent rationalisation of antibiotic regimen [2, 7–9]. Although data from the 1990s suggested bronchoscopy did not often lead to a change in therapeutic strategy, more recent studies have shown that bronchoscopy results in an altered antibiotic regimen around 38% of the time and treatment plan 81% of the time in patients with haematological malignancy and lung infection [6, 10]. Recent advances in antimicrobials, assay development and pathogen classification has led to increased regimen complexity. Tissue diagnosis enables changes to targeted therapies with cessation of empirical agents. Narrowing the antimicrobial spectrum from multiple agents brings better tolerability for patients, less interaction with chemotherapy agents and other drugs, less stimulus of resistant organisms and lower healthcare-associated costs.

Conclusion

Although clinicians may be reluctant to request or perform bronchoscopy on patients with haematological malignancy, it remains a safe and essential tool for specific diagnosis of causative organisms in the vulnerable oncohaematological population. Specific diagnosis and subsequent

pathogen-targeted treatment is more important than ever, with the increasing prevalence of MDROs. Since the prevention and early effective treatment of opportunistic infection is equally as important as targeted chemotherapy to patient survival, bronchoscopy should be recognised as an essential tool in the investigation of unexplained pulmonary infiltrates in this setting.

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Conflict of interest

None declared.

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