Pro/con debate

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

Introduction

Pulmonary infiltrates occur commonly in populations with haematological malignancy and are associated with high rates of morbidity and mortality [1–5]. There is a wide differential diagnosis for these infiltrates of which ~70% are infective in nature [6]. Tools available to the bronchoscopist to evaluate these patients include standard bronchial washings, bronchoalveolar lavage (BAL), protected specimen brushes and transbronchial lung biopsy and the prevailing body of literature suggests that bronchoscopy, when employed with a variety of these tools, can help identify culprit organisms in around half of these cases. However, in order to assert that bronchoscopy is an essential procedure in the setting of pulmonary infections in patients with haematological malignancy, one would need to provide a convincing argument that the procedure is safe, provides a high diagnostic yield and reliably leads to a change in management that positively influences patient outcome and pre-eminently survival. Unfortunately, despite a plethora of retrospective, single centre, nonrandomised and noncontrolled studies, the literature suffers a dearth of well-designed and rigorously conducted prospective clinical trials in this population and the risk of positive publication bias is real, with negative studies less likely to be published [7, 8].

The development of an increasing array of noninvasive investigations to identify culprit organisms reduces the reliance on bronchoscopic sampling, which developed at a time when few alternatives were available. The widespread use of legitimately directed prophylactic and empiric antibiotics successfully prevents and manages many of these infections without needing to resort to an invasive strategy such as bronchoscopy and these same antibiotics reduce diagnostic yield of the procedure. Whilst most studies claim that bronchoscopy leads to a change in clinical management, mostly through addition or cessation of antimicrobials, there is limited quality data to suggest that this translates into meaningful improved clinical outcome. Finally, haematological patients with pulmonary infiltrates are often unstable and at high risk of deterioration and the risk–benefit profile of an invasive procedure must be carefully weighed, with particular cognisance of the deleterious effects of respiratory failure following bronchoscopy, resulting in invasive ventilation with attendant high mortality rates.

Noninvasive testing

Minimally invasive strategies to aid the diagnosis of infectious aetiologies can avoid the need for more invasive procedures such as bronchoscopy. Use of thoracic imaging, particularly computed tomography, is common in this patient population and has been shown to demonstrate pathological findings more often than chest radiographs [1, 9]. The distribution and morphology of pulmonary infiltrates can...
help provide a plausible differential diagnosis [1]. Pathognomonic radiological signs such as the “halo sign” or “reversed halo sign” and nodular cavitory lesions strongly suggest fungal disease, while diffuse bilateral, peripheral sparing, perihilar infiltrates may indicate pneumocystis [9]. In many circumstances typical chest imaging may direct empirical therapy without need for further investigations [1].

In addition to imaging, there is an increasing array of available serological and microbiological investigations that may also inform the diagnosis of pulmonary infiltrates. Pathogens have been typically isolated in culture-based respiratory, nasopharyngeal and blood specimens. However, recent advances in molecular testing, including various antigen testing and nucleic acid-based assays, have optimised noninvasive diagnostic strategies [1, 5, 10]. The technique of specimen collection also plays a role with induced sputum samples providing a microbiological diagnosis in up to 60–80% of cases, increasing with repeated inductions [11].

Non-culture-based assays can be performed on wide variety of specimens that include sputum, induced sputum, nasopharyngeal aspirates, serum and urine. A combination of investigations should be requested based on patient risk factors, local epidemiological factors and likelihood of an atypical pathogen. Serum antigens such as Aspergillus galactomannan has a reported sensitivity of 38–78% [12, 13], while beta-D glucan, cryptococcal and histoplasma may also be instructive [1, 5]. Urinary antigen tests may diagnose Legionella pneumophila, Blastomyces dermatitidis and Streptococcus pneumoniae infections. Importantly, it has been shown that optimal quality and rapidly collected samples aid in increasing noninvasive diagnostic yield [10].

One study that retrospectively examined multiple noninvasive diagnostic tools in immunocompromised haematological patients showed a diagnostic yield of ~69% compared with BAL alone (31%) [14]. In addition, a randomised trial comparing noninvasive testing alone or coupled with bronchoscopy and BAL in non-intubated haematology or oncology patients demonstrated noninvasive diagnostic tests had a higher diagnostic yield [4].

**Diagnostic yield**

There is a paucity of clinical trials that examine the diagnostic yield of bronchoscopy in haematological malignancies and pulmonary infiltrates. Most of the evidence is retrospective, and the overall diagnostic yield of bronchoscopy varies widely from 23% to 65% due to a combination of patient heterogeneity, sampling techniques and timing [1, 15–18].

Pulmonary infections are overwhelmingly associated with mortality and morbidity in this population, which has led to the routine use of prophylactic antibacterial, antiviral and antifungal regimens. In combination with empirical antimicrobial therapy often commenced prior to bronchoscopy, these antimicrobials may reduce diagnostic yield. In a study that retrospectively examined bronchoscopic diagnosis of pulmonary infiltrates in haematopoietic stem cell transplant (SCT), the yield was over two times higher among bronchoscopies performed within the first 4 days of presentation and highest (75%) when performed within 24 h of clinical presentation [6]. This is supported by further studies that confirm greater diagnostic yields in patients on antibiotics for <24 h or on no antimicrobials [14, 19].

Furthermore, diagnostic yield may correlate with anatomic location of pulmonary infiltrates and may also be higher in patients who are symptomatic and febrile compared with those who are asymptomatic [1]. Sampling techniques such as transbronchial lung biopsy or brushings combined with BAL improve diagnostic rates but need to be balanced against increased complication rates [15].

Importantly, the finding of one or more organisms in BAL culture does not necessarily indicate the cause of the infection and interpretation of results can be difficult especially in immunosuppressed populations where polymicrobial infections are common, commensal organisms are frequently noted and post-mortem studies do not always correlate with pre-mortem findings [20, 21].

**Lack of therapeutic impact**

Quality data concerning positive therapeutic benefit attributable to bronchoscopy are limited and results from the literature are mixed. The frequency with which BAL-derived results lead to demonstrable changes in antimicrobial therapy in haematological patients varies widely (20–70%) [1, 5], and the subjectivity of what constitutes a useful change in treatment coupled with the lack of good quality prospective data limits how we should interpret this outcome. It should also be emphasised that a change in clinical management is a poor surrogate for clinical utility and that more rigorous and meaningful outcomes should include recovery from infection or survival at a predefined time-point, but again the literature fails to address these definitively.

Gruson et al. [20] demonstrated in a retrospective analysis of a prospectively collected cohort of 93 intensive care unit (ICU) patients with neutropenic respiratory sepsis associated with haematological malignancy, that despite a reasonable diagnostic yield of 49%, and even in those where the BAL led to a change in antimicrobial therapy, there was no survival benefit, casting doubt on the clinical utility of the procedure. Hofmeister et al. [22] found similarly discouraging results in SCT recipients noting that resistant pseudomonal species were often identified and that extending the spectrum of antibiotic coverage in patients who...
failed to respond to initial empiric antibiotics would be an alternate strategy to subjecting the patient to an invasive procedure. In a multicentre cohort of 128 haematology and oncology patients admitted to the ICU with acute respiratory failure, overall mortality was not influenced by a diagnostic strategy involving bronchoscopy versus no bronchoscopy. There is some suggestion that survival in patients with SCT may be improved if BAL is performed within 4 days of presentation compared with bronchoscopy performed after 4 days (mortality 6% early versus 18% late, p=0.0351), but again conclusions are difficult to draw from data where the timing of bronchoscopy was not randomised or controlled [6]. Similar limitations hampered a single centre study in SCT recipients, 40 of whom underwent either early (≤5 days) or late (>5 days) bronchoscopy for pulmonary complications. Yield was higher in the early group (78% versus 23%; p=0.02) but this did not result in a difference in antimicrobial therapy [23].

A prospective study by Marchesi et al. [2] purported a survival benefit at 120 days in patients in whom a BAL-driven antibiotic regimen was used compared with patients in whom BAL did not influence the antibiotic regimen (due to lack of finding a culprit organism or lack of treatable organism, e.g. virus). However, it is not possible to confirm that the BAL findings themselves resulted in improved survival as opposed to identifying a group with an infectious aetiology more likely to respond to antimicrobials. The fact that the opposite result was found in another prospective study suggests that until we can randomise patients to a bronchoscopy versus non-bronchoscopy strategy, the true influence of bronchoscopy will remain unanswered [24].

**Bronchoscopy complications**

In a retrospective review of 217 patients with immunosuppression and pulmonary infiltrates, Choo et al. [25] reported a 90-day mortality rate in haematology patients over twice that in non-haematological malignancies and over four times that in patients with HIV (28.3% versus 12.1% versus 6.8%, respectively). Accordingly, the risks associated with subjecting these patients to bronchoscopy require careful justification. In the ICU setting, Gruson et al. [20] reported a bronchoscopy complication rate of 17% (16 out of 93 patients) with two patients requiring invasive ventilation and another four requiring noninvasive ventilation. Further, the overall mortality of the cohort was 71% raising serious questions about the prudence of bronchoscopy in this high-risk cohort [20]. Complication rates vary widely in the published literature between 1% and 52% [6, 24–28], making interpretation difficult for local institutions. However, most would agree that in the setting of acute respiratory failure (ARF), the risks of bronchoscopy are extreme. Rabbat et al. [29] reported on 175 haematological patients admitted to the ICU for ARF undergoing bronchoscopy noting a 10% rate of life-threatening complications. While the diagnostic yield was reasonable at 50%, this influenced the therapeutic decisions in only 17%. Another study of 148 ICU patients with cancer (122 with haematological malignancies) and respiratory failure noted deterioration in respiratory status following bronchoscopy in 48.9% of non-intubated patients (requiring escalation of ventilatory support in 35.5%). Further, in this cohort, bronchoscopy itself independently predicted a need for conventional mechanical ventilation (OR 14.73, 95% CI 4.27–50.83; p 0.0001) [30]. The risks of bronchoscopy are lower in less unwell haematology populations but even this risk must be justified by evidence that is currently lacking.

**Conclusion and a way forward**

We have identified sufficient shortcomings in the available literature to strongly argue against the role of bronchoscopy as an essential investigation for all pulmonary infections in patients with haematological malignancies.

We believe there is a justifiable argument to advocate for a multicentre prospective controlled trial with patients randomised to a “bronchoscopy” versus “no bronchoscopy” arm with strict inclusion criteria, a uniform panel of noninvasive tests and an escalating antimicrobial panel in the “no bronchoscopy” arm in lieu of BAL. In addition, stringent timing of the bronchoscopy and a protocled sampling technique should be employed to decrease confounding factors that cloud conclusions drawn from previous retrospective data. Furthermore, predefined outcome criteria including not only yield and safely, but more importantly resolution of infection and preferably an effect on survival would be highly valued.

However, until such a trial is performed, the literature does suggest a cohort of haematological patients who may potentially benefit from BAL, which would include patients with early onset of infection (within 4 days but ideally within 24 h), preferably prior to empirical antimicrobials and in those with sufficient respiratory reserve to tolerate the procedure safely. Prior to bronchoscopy, extensive use of noninvasive diagnostic investigations is essential, and in many cases will be able to circumvent the need for an invasive procedure. Local resources and expertise obviously influence such an approach and not all centres have access to a timely bronchoscopy service. Therefore, a tailored approach by each centre is needed.

In summary, while some patients with haematological malignancy and pulmonary infection may benefit from a bronchoscopy, the uniform adoption of this approach is in no way justified by the literature, and much needed studies are required to fill the void in our understanding of this area.
Con: Bronchoscopy, infection and haematological malignancy

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Conflict of interest
None declared.

References