Matthew K. Ing[1], Jonathan P. Williamson[1,2,3]

Matthew.Ing@health.nsw.gov

Pro/con debate

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

Cite as: Ing MK, Williamson JP. Con: Bronchoscopy is essential for pulmonary infections in patients with haematological malignancies. *Breathe* 2020; 16: 200210.

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

@ERSpublications
Whilst some patients with haematological malignancy and pulmonary infection may benefit from a bronchoscopy, this uniform approach is not justified by the literature and more studies are required to fill the void in our understanding of this area https://bit.ly/3bfUfs7

help provide a plausible differential diagnosis [1]. Pathognomonic radiological signs such as the "halo sign" or "reversed halo sign" and nodular cavitary 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 protocoled 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.

Affiliations

Matthew K. Ing[1], Jonathan P. Williamson[1,2,3]

[1]Dept of Respiratory Medicine, Liverpool Hospital, Sydney, Australia. [2]South Western Sydney Clinical School, Liverpool Hospital, The University of New South Wales, Sydney, Australia. [3]MQ Health Respiratory and Sleep, Macquarie University Hospital, Sydney, Australia.

Conflict of interest

None declared.

References

1. Harris B, Geyer AI. Diagnostic evaluation of pulmonary abnormalities in patients with hematologic malignancies and hematopoietic cell transplantation. *Clin Chest Med* 2017; 38: 317–331.
2. Marchesi F, Cattaneo C, Criscuolo M, *et al.* A bronchoalveolar lavage-driven antimicrobial treatment improves survival in hematologic malignancy patients with detected lung infiltrates: A prospective multicenter study of the SEIFEM group. *Am J Hematol* 2019; 94: 1104–1112.
3. Choi MH, Jung JI, Chung WD, *et al.* Acute pulmonary complications in patients with hematologic malignancies. *Radiographics* 2014; 34: 1755–1768.
4. Azoulay E, Mokart D, Lambert J, *et al.* Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. *Am J Respir Crit Care Med* 2010; 182: 1038–1046.
5. Camous L, Lemiale V, Kouatchet A, *et al.* Minimally Invasive Diagnostic Strategy in Immunocompromised Patients with Pulmonary Infiltrates. *In:* E Azoulay, ed. *Pulmonary Involvement in Patients with Hematological Malignancies*. Berlin, Springer, 2011; pp. 175–189.
6. Shannon VR, Andersson BS, Lei X, *et al.* Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2010; 45: 647–655.
7. DeVito NJ, Goldacre B. Catalogue of bias: publication bias. *BMJ Evid Based Med* 2019; 24: 53.
8. Fanelli D. Positive results receive more citations, but only in some disciplines. *Scientometrics* 2013; 94: 701–709.
9. Maschmeyer G, Carratala J, Buchheidt D, *et al.* Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Oncol* 2015; 26: 21–33.
10. Danés C, González-Martín J, Pumarola T, *et al.* Pulmonary infiltrates in immunosuppressed patients: analysis of a diagnostic protocol. *J Clin Microbiol* 2002; 40: 2134.
11. Menzies D. Sputum induction. *Am J Respir Crit Care Med* 2003; 167: 676–677.
12. Leeflang MMG, Debets-Ossenkopp YJ, Visser CE, *et al.* Galactomannan detection for invasive aspergillosis in immunocompromised patients. *Cochrane Database Syst Rev* 2015; 2015: CD007394.
13. Park SY, Lee SO, Choi SH, *et al.* Serum and bronchoalveolar lavage fluid galactomannan assays in patients with pulmonary aspergilloma. *Clin Infect Dis* 2011; 52: e149–e152.
14. Hohenadel IA, Kiworr M, Genitsariotis R, *et al.* Role of bronchoalveolar lavage in immunocompromised patients with pneumonia treated with a broad spectrum antibiotic and antifungal regimen. *Thorax* 2001; 56: 115.
15. Morton C, Puchalski J. The utility of bronchoscopy in immunocompromised patients: a review. *J Thorac Dis* 2019; 11: 5603–5612.
16. Kim S, Rhee CK, Kang HS, *et al.* Diagnostic value of bronchoscopy in patients with hematologic malignancy and pulmonary infiltrates. *Ann Hematol* 2015; 94: 153–159.
17. Seneviratna A, O'Carroll M, Lewis CA, *et al.* Diagnostic yield of bronchoscopic sampling in febrile neutropenic patients with pulmonary infiltrate and haematological disorders. *Intern Med J* 2012; 42: 536–541.
18. Jorge L, Torres D, Languasco A, *et al.* Clinical usefulness of bronchoalveolar lavage in the management of pulmonary infiltrates in adults with hematological malignancies and stem cell transplantation. *Mediterr J Hematol Infect Dis* 2020; 12: e2020025.
19. Yacoub AT, Thomas D, Yuan C, *et al.* Diagnostic value of bronchoalveolar lavage in leukemic and bone marrow transplant patients: the impact of antimicrobial therapy. *Mediterr J Hematol Infect Dis* 2015; 7: e2015002.
20. Gruson D, Hilbert G, Valentino R, *et al.* Utility of fiberoptic bronchoscopy in neutropenic patients admitted to the intensive care unit with pulmonary infiltrates. *Crit Care Med* 2000; 28: 2224–2230.
21. Cordonnier C, Escudier E, Verra F, *et al.* Bronchoalveolar lavage during neutropenic episodes: diagnostic yield and cellular pattern. *Eur Respir J* 1994; 7: 114.
22. Hofmeister CC, Czerlanis C, Forsythe S, *et al.* Retrospective utility of bronchoscopy after hematopoietic stem cell transplant. *Bone Marrow Transplant* 2006; 38: 693–698.
23. Lucena CM, Torres A, Rovira M, *et al.* Pulmonary complications in hematopoietic SCT: a prospective study. *Bone Marrow Transplant* 2014; 49: 1293–1299.
24. Sampsonas F, Kontoyiannis DP, Dickey BF, *et al.* Performance of a standardized bronchoalveolar lavage protocol in a comprehensive cancer center a prospective 2-year study. *Cancer* 2011; 117: 3424–3433.
25. Choo R, Naser NSH, Nadkarni NV, *et al.* Utility of bronchoalveolar lavage in the management of immunocompromised patients presenting with lung infiltrates. *BMC Pulm Med* 2019; 19: 51.
26. Burger CD. Utility of positive bronchoalveolar lavage in predicting respiratory failure after hematopoietic stem cell transplantation: a retrospective analysis. *Transplant Proc* 2007; 39: 1623–1625.
27. Hummel M, Rudert S, Hof H, *et al.* Diagnostic yield of bronchoscopy with bronchoalveolar lavage in febrile patients with hematologic malignancies and pulmonary infiltrates. *Ann Hematol* 2008; 87: 291–297.
28. Gilbert CR, Lerner A, Baram M, *et al.* Utility of flexible bronchoscopy in the evaluation of pulmonary infiltrates in the hematopoietic stem cell transplant population – a single center fourteen year experience. *Arch Bronconeumol* 2013; 49: 189–195.
29. Rabbat A, Chaoui D, Lefebvre A, *et al.* Is BAL useful in patients with acute myeloid leukemia admitted in ICU for severe respiratory complications? *Leukemia* 2008; 22: 1361–1367.
30. Azoulay E, Mokart D, Rabbat A. Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: prospective multicenter data. *Crit Care Med* 2008; 36: 100–107.