

Use of bronchoscopy in the diagnosis of infection in the immunocompromised host

Although studies have shown the usefulness of individual methods such as bronchoalveolar lavage (BAL) in diagnosing pneumonia,^{1,2} the bronchoscope itself provides access to lower respiratory secretions and tissue in a number of ways.

Bronchoscopy allows us to sample the lower respiratory tract by (1) bronchial washings, which are a pooling of the secretions retrieved during bronchoscopy; (2) BAL, during which fluid is collected by low pressure suction after a fairly large volume (100–240 ml) of saline is instilled and aspirated at low pressure with the bronchoscope wedged in a distal airway; (3) bronchial brushing, during which a catheter is advanced into a specific area of the lung and samples are taken; and (4) biopsy, in which a small amount of tissue from the airway (bronchial biopsy) or alveolar space (transbronchial biopsy) is sampled. These techniques are complementary for diagnosing many infections, although one or other procedure may be better suited for individual infections. For example, bronchial brushing and biopsies increase the chances of bleeding during the procedure and are not usually performed in thrombocytopenic patients,³ and transbronchial biopsy has a significantly higher risk of causing pneumothorax than bronchoscopy alone, although the risk is still less than 10%.³⁻⁵

In assessing the various techniques one has to consider that certain infections may be more likely to be diagnosed by one technique than by another. The techniques sample different portions of the airways and thus what they diagnose depends somewhat on where the microorganism resides. For example, *Pneumocystis carinii* is present in alveoli and is best diagnosed by techniques which sample the alveoli (BAL) or allow for direct pathological examination (transbronchial biopsy).⁴ Bronchial brushing will not reach the alveoli and therefore is not going to be diagnostic for most cases of *P. carinii*. On the other hand, *Mycobacterium tuberculosis* is present in cavities and in the airways; BAL may not sample a thin walled cavity easily, while bronchial washing samples the airway secretions better than does BAL.⁶

Another concern is the significance of a particular pathogen. The recovery of some organisms from any respiratory secretion is clearly associated with pneumonia (for example, *M. tuberculosis* or *P. carinii*),^{1,2,4,6} while other organisms such as *Candida* and *Streptococcus pneumoniae* may colonise the upper airway without necessarily causing disease. In the latter case pathological changes need to be shown in the lower respiratory tract by cytological or histopathological examination, or the organism must be recovered at higher concentrations in the lower than the upper airway.⁷

In the following sections individual infections and how they are best diagnosed by bronchoscopy are discussed.

Pneumocystis pneumonia

For patients with possible pneumocystis pneumonia bronchoscopy is the procedure with the highest yield and the lowest risk. Diagnosis of pneumocystis pneumonia by induced sputum has been proposed as an alternative method with lower cost and reasonable sensitivity.⁸⁻¹¹ However, the cost of processing the specimen has to be

included, and a laboratory highly familiar with the correct identification is needed; there is also the complication of multiple infections being present. In our experience of over 400 HIV patients infected with pneumocystis pneumonia an additional pathogen has been found in over 15% of cases.

There have been several comparisons of the different methods of diagnosing pneumocystis pneumonia by bronchoscopy (table 1). Bronchial brushing has the lowest diagnostic yield, significantly less than either BAL or transbronchial biopsy. This is probably because the alveolar sample is diluted with upper airway secretions which have very few organisms.

Transbronchial biopsy consistently has the highest yield of organisms. To be diagnostic, several biopsies with alveolar tissue have to be obtained. Rarely is *P. carinii* seen in bronchial biopsies¹⁷ and, because of the need for alveolar sampling, there is a significant risk of pneumothorax developing. This is a considerable problem in patients with pneumocystis pneumonia who already have an increased risk for spontaneous pneumothoraces.^{18,19} In a study of over 100 HIV infected patients undergoing transbronchial biopsy, 9% had pneumothoraces and over half of these required chest drainage.⁴

Bronchoalveolar lavage appears to have a sufficiently high diagnostic yield, good specificity, and relatively low morbidity compared with transbronchial biopsy. It is now the procedure of choice for diagnosing pneumocystis pneumonia,²⁰ with most centres no longer performing transbronchial biopsies. In addition to identifying the organism, BAL provides additional information including an assessment of the inflammatory response of the lung. Patients with pneumocystis pneumonia have increased levels of neutrophils in their BAL fluid, with increased albumin permeability and a poorer prognosis.^{21,22} Bronchoalveolar lavage can also estimate the relative burden of *P. carinii* infection in the lung,^{23,24} and this has been used to determine the response to drug treatment.²⁵

Jules-Elysee and colleagues¹² reported that BAL may have only a 60% diagnostic yield in patients receiving treatment with aerosolised pentamidine; in such patients the transbronchial biopsy significantly enhances diagnostic yield. Since aerosolised pentamidine is associated with a significant failure rate,²⁶ there is concern that, in the HIV patient with possible pneumocystis pneumonia, the diagnosis may be missed if only BAL is performed. We²⁷ and others²⁸⁻³⁰ have shown that lavaging areas with most

Table 1 Relative efficacy (%) of various bronchoscopic techniques for diagnosing *Pneumocystis carinii* pneumonia in patients with AIDS

Reference	No. of cases	Brushing	Washing	Bronchoalveolar lavage	Biopsy
Broaddus <i>et al</i> ⁴	117			89	93
Jules-Elysee <i>et al</i> ¹²					
No pentamidine	31			100	84
Pentamidine prophylaxis	21			62	81
Gal <i>et al</i> ¹³	20	79		95	94
Baughman <i>et al</i> ¹⁴	59		70	97	
Coleman <i>et al</i> ¹⁵	22	39	55		79
Stover <i>et al</i> ¹⁶	39		41	85	88
Mones <i>et al</i> ¹⁷	95	57	59		97
Total	404	58	58	90	91

infiltrate on the chest radiograph can enhance the diagnostic yield. There are generally about twice as many organisms in the upper lobe than in the middle lobe of patients with pneumocystis pneumonia.^{27,29}

Viral infections

In the immunocompetent patient cytomegalovirus (CMV) pneumonia is rare. Even in patients with CMV viraemia resulting from post transfusion infection pneumonia is uncommon. However, in the immunocompromised patient CMV can be dangerous, even fatal, particularly in patients with bone marrow transplantation. The infection usually occurs 6–8 weeks after the transplantation.^{31,32} The patient may develop acute pneumonia or a more indolent infection, which may lead to a graft versus host reaction in the lung.³³ This pneumonitis can be progressive and may not respond to antiviral treatment such as ganciclovir alone.³⁴ Because of the poor prognosis of patients with advanced disease, attempts have been made to make an early, precise diagnosis in these patients.

The highest diagnostic yield for CMV infection is from the BAL fluid. Unfortunately it may be several weeks before final culture results are available, but more rapid results can be obtained by identifying antigenic changes in infected cells using BAL or bronchial washing.^{35,36} These will identify >80% of specimens which subsequently will be culture positive, and can be enhanced by the shell vial centrifugation technique with results available within one day.^{35,37,38}

In patients with solid organ transplants the presence of CMV in the lower respiratory tract is less significant, but is still a problem.^{31,39,40} Lung transplant patients can develop a reaction which is equivalent to the graft versus host reaction seen in bone marrow transplant patients. It has been proposed that CMV infection is responsible for the bronchiolitis obliterans associated with chronic rejection.⁴¹ In other solid organ transplants CMV infection can range from mild to severe.^{40,42}

In the HIV infected population CMV is commonly recovered from culture of the BAL fluid specimen.^{43–45} This is associated with more severe hypoxaemia but there is no evidence of any short term (less than three weeks) increase in mortality for HIV positive patients with CMV infection. However, necropsy studies have shown that patients do die from CMV pneumonitis.⁴⁶

To determine whether a patient has CMV pneumonia rather than just infection, the most specific method is transbronchial biopsy looking for cytopathological changes with an associated pneumonitis.³⁹ The examination of BAL fluid and wash specimens may also demonstrate more advanced lower respiratory infection, but may not be as specific as the transbronchial biopsy specimen. Cytological diagnosis can be performed on the brushings, washings, or BAL fluid specimens, with BAL fluid having a higher diagnostic yield for CMV; however, in our laboratory BAL and washing are complementary. In situ hybridisation can also be used to detect CMV genomic material in individual cells,⁴⁷ but it is not clear whether these changes correspond to CMV pneumonitis.

Herpes simplex virus (HSV) is not a significant pathogen in immunocompromised patients but it can cause pneumonia.⁴⁸ Reactivation of upper airway herpes virus is not uncommon during stress. In patients with the adult respiratory distress syndrome (ARDS) the recovery of HSV from bronchoscopy washes was associated with a higher rate of mortality.⁴⁹ A subsequent study showed that prophylactic acyclovir could reduce the incidence of HSV infection but it did not change the morbidity or mortality of the underlying ARDS.⁵⁰ Cytological examination speci-

mens can be helpful, and lesions suspicious for HSV in the airways can be specifically diagnosed by bronchial brushing and subsequent Papanicolaou staining to show giant cells with inclusion bodies.

The recovery of other viruses by bronchoscopy has occasionally been reported. In a study of over 1000 BAL fluid samples cultured for viruses at our institution, one or more viruses were identified from over 50%.⁵¹ The most common were CMV and HSV, comprising 550 cases, and other viruses included influenza, parainfluenza, adenovirus, and rhinovirus. Only the influenza and adenovirus appeared to be associated with significant morbidity.

Tuberculosis

Although sputum sampling remains the procedure of choice for diagnosing tuberculosis,⁵² the use of bronchoscopy has become common, especially in immunocompromised patients. Bronchial washing, BAL, and transbronchial biopsy have all been studied.^{6,53,54} The techniques appear complementary, although my personal feeling is that bronchial washing provides the safest, highest diagnostic yield. In the study by Wallace *et al*⁵⁴ transbronchial biopsy significantly enhanced the diagnostic yield from bronchial washing alone. In our study of 50 patients with *M tuberculosis* infection we rarely found it necessary to perform a transbronchial biopsy; seven patients had a positive wash specimen and negative BAL fluid specimen, and only one patient had the reverse.⁶ The higher yield from bronchial washing in our study may have been because of the larger sample obtained, as the washing included fluid not aspirated during the BAL technique itself. In patients with cavities BAL may have a poor result because of airway collapse during aspiration; however, lavage itself will induce cough and the subsequent specimen should contain plenty of organisms (the ultimate in saline induced sputum).

Fungal infections

Histoplasmosis, coccidiomycosis, and cryptococcus have all been isolated from bronchoscopy specimens.^{6,55,56} The overall diagnostic yield for these pathogens by culture, however, may be less than that obtained in tuberculosis.

The bronchial washing specimen has been shown to have a good yield in patients with fungal infection.^{6,55,57} Cultures are more sensitive than direct cytological examination. The BAL fluid specimen may increase the yield for pathogens, both for the BAL itself and by increasing the volume of the wash specimen. Transbronchial biopsy can

Table 2 Comparison of various bronchoscopic techniques to identify individual organisms on a scale of 0–3

Organism	Washing	Brushing	Broncho-alveolar lavage	Biopsy	References
<i>Pneumocystis carinii</i>	2	1	3	3	4,12,13,14,27
Viral					
Cytomegalovirus	1	1	3	2	36,37,38,45
Other viral	1	1	2	1	51
Tuberculosis	3	0	2	3	6,53,54
Fungal					
<i>Candida</i>	0	0	1	2	60
<i>Aspergillus</i>	0	0	1	2	60
Histoplasmosis, blastomycosis, cryptococcus, coccidiomycosis	2	1	2	1	6,55,56,57
Bacterial					
Routine bacterial	0	3*	2	0	7,63,69,75
<i>Legionella</i>	1	1	2	1	78,79
<i>Nocardia</i>	3	ND	2	ND	55,80

ND = Not determined.

* Protected brush.

Table 3 Relative risk of infection based on underlying condition of host on scale of 0-3

	HIV infected			Transplantation	
	> 250 CD4 lymphocytes/mm ³	< 250 CD4 lymphocytes/mm ³	Neutropenic	Solid organ	Bone marrow
<i>Pneumocystis carinii</i>	1	3	2	2	1
<i>Mycobacterium tuberculosis</i>	3	1	1	1	1
Routine bacterial	2	1	2	2	2
<i>Legionella</i>	0	0	0	2	2
<i>Candida/Aspergillus</i>	0	0	2	0	2
Histoplasmosis, coccidiomycosis, cryptococcus	2	3	2	1	1
Cytomegalovirus	1	2	2	2	3

define whether there is fungus within the lower respiratory tract but the amount of tissue available for culture is small. In an animal model of histoplasmosis BAL was found to be more sensitive than transbronchial biopsy in diagnosing pulmonary histoplasmosis;⁵⁶ thus, there appears to be a limited role for transbronchial biopsy in these infections.

Another option for rapid diagnosis of fungi is to look for antigens. Cryptococcal antigen is detectable in the BAL fluid,⁵⁸ a titre of $\geq 1:8$ being associated with positive culture. A histoplasmosis antigen has also been reported in the BAL fluid,⁵⁹ but this test is not as widely available as the cryptococcal antigen test. The use of these antigen tests should be selective. We examine for cryptococcal antigen in our HIV infected patients as they are at high risk for this since infection and the test can be run in less than one hour.

For *Candida* and *Aspergillus* infections there are two issues. Firstly, the organisms are less sensitive to cell mediated immunity and are more likely to be controlled by neutrophils, so they are rarely encountered unless there has been neutropenia, use of broad spectrum antibiotics, diabetes, or treatment with corticosteroids. Here the concern is that *Candida* or *Aspergillus* may become invasive with associated significant morbidity and mortality. Secondly, in diagnosing candidal or aspergillus pneumonia the recovery of pathogen by bronchial washing or BAL is insufficient. If a large number of fungi are seen in a BAL fluid specimen, one could argue that the infection is more than upper airway colonisation,⁶⁰ but this assumption has not been rigorously tested. A more specific diagnosis can be made by examining a transbronchial biopsy, as the presence of invasive organisms confirms infection.⁶¹ Unfortunately, many patients with possible infection with *Aspergillus* are not only neutropenic but thrombocytopenic, and thus cannot undergo a biopsy.

Bacterial pneumonia

Historically, bronchoscopy was considered a poor method of diagnosing bacterial pneumonia⁶² because the lower respiratory tract becomes contaminated during the bronchoscopy itself. The upper airway secretions contaminate the bronchoscope, as well as contaminating the lower respiratory system. The culturing of bronchial washings is therefore not useful.

To circumvent the upper respiratory contamination two methods are used. The first is the protected specimen brush first described by Wimberley *et al.*⁶³ Unfortunately this technique does not always provide a sterile sample in the uninfected host, and quantitation of the organisms recovered is necessary to determine whether the organism is an upper respiratory contaminant or represents lower respiratory infection.^{64,65} The specimen is resuspended in a known volume of fluid and cultures are performed in a semiquantitative manner. Using the semiquantitative cutoff of $\geq 10^3$ colony forming units (cfu)/ml of resuspended specimen, sensitivity and specificity of over 80% are achieved in patients not receiving antibiotics.⁶⁶ This includes patients with community acquired pneumonia,⁶⁷

sickle cell disease,⁶⁸ those on mechanical ventilation,⁶⁹⁻⁷² renal transplantation,⁶¹ and other immunocompromised patients.^{73,74}

Bronchoalveolar lavage has also been used to acquire a relatively clean sample from the lower respiratory tract, and it allows sampling of a wider area of the lung. This, at least theoretically, should be more sensitive than the brush technique. In a prospective study of patients undergoing bronchoscopy⁷ there were 54 patients with no clinical evidence of bacterial pneumonia. The semiquantitative culture recovered $< 10^4$ cfu/ml BAL fluid from 50 of the 54 patients (93%), while none of the non-infected patients had $> 10^5$ cfu/ml BAL fluid. In patients with a bacterial pneumonia not responding to antibiotics, 13 of 15 (86%) had $> 10^5$ cfu/ml and the remaining two grew between 10^4 and 10^5 cfu/ml. The distinction between pneumonia and non-pneumonia on the basis of semiquantitative cultures has been confirmed by other groups.^{66,75,76} In general, if the patient has $> 10^5$ cfu/ml then he has pneumonia, but with $< 10^4$ cfu/ml he does not. It is not known whether a protected BAL catheter improves the specificity of the procedure.⁷⁷

Legionella and *Nocardia* are bacterial pathogens whose recovery from sputum is unusual. Bronchoscopy is a suitable method for diagnosing both of these pathogens.^{55,78,79} Our experience with 11 patients with nocardial pneumonia showed that both bronchial washing and BAL could be diagnostic, and the organism was usually identified in fungal culture media.⁸⁰ *Legionella* is best recovered from a non-selective, highly enriched charcoal media from the BAL fluid.⁷⁹

Conclusion

Non-infectious causes of infiltrates and hypoxaemia that can be diagnosed by bronchoscopy have not been discussed. These include pulmonary haemorrhage, malignancy, and hypersensitivity reactions.

The use of bronchoscopy for diagnosing infection has become routine in pulmonary medicine. Each of the sampling techniques has a role for individual organisms, with some techniques having a wider range of success than others. Table 2 summarises the various pathogens found in the lower respiratory tract and the relative diagnostic value of each technique. Table 3 is a summary of the risk of infection, dependent on the underlying condition of the host. These two tables can be used as a guide to determine which specimens to obtain during bronchoscopy. For example, a transbronchial biopsy is of limited value in the initial assessment of ventilator associated pneumonia, while it may be necessary in the HIV infected patient in whom CMV pneumonitis is suspected.

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