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Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL versus PSB and PBAL

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Summary
Background: Treatment of patients with hematologic malignancies is often complicated by severe respiratory infections. Bronchoscopy is generally to be used as a diagnostic tool in order to find a causative pathogen.
Objectives: In a prospective study the combination of protected specimen brush (PSB) and protected bronchoalveolar lavage (PBAL) was compared with bronchoalveolar lavage (BAL) for evaluated feasibility and diagnostic yield in granulocytopenic patients with hematologic malignancies and pulmonary infiltrates.
Methods: All specimens from 63 bronchoscopic procedures (35 BAL and 28 PSB-PBAL) were investigated by cytological examination and various microbiological tests. If clinically relevant and feasible, based on the clinical condition and/or the presence of thrombocytopenia, lung tissue samples were obtained.
Results: The majority of the 58 included patients were diagnosed as having acute myeloid leukaemia and developed a severe neutropenia (BAL-group: 27 days; PSB-PBAL group: 30 days). Microbiological and cytological examination of 63 bronchoscopic procedures (35 BAL and 28 PSB-PBAL) yielded causative pathogens in 9 (26%) patients of the BAL-group and 8 (29%) patients of the PSB-PBAL group (PSB and PBAL 4 each). *Aspergillus fumigatus* was the pathogen most frequently (13%) detected.

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Using all available examinations including the results of autopsy, a presumptive diagnosis was established in 43% of the patients in the BAL group and 57% of those in the PSB-PBAL group; in these cases microbial aetiology was correctly identified in 67% and 57%, respectively. The complication rate was of these procedures were low, and none of the patients experienced serious complications due to the invasive techniques.

Conclusions: Our results showed that modern bronchoscopic techniques such as PSB and PBAL did not yield better diagnostic results compared to BAL in granulocytopenic patients with hematologic malignancies and pulmonary infiltrates. In approximately half of the cases a presumptive diagnosis was made by bronchoscopic procedures.

Introduction

Respiratory infections, particularly pneumonia, constitute a major threat to the immunocompromised patient. Patients with hematologic malignancies and prolonged neutropenia are at the highest risk for acquiring invasive infections, associated with a high mortality. In these patients, diagnostic problems due to several factors such as the patient's critical condition, the presence of multiple infections, and the previous use of empirical antibiotic therapy, are frequently observed. Febrile episodes are a rule rather than the exception in patients being intensively treated for leukaemia and lymphoma.[1] Boggs and Friedland[2] reported 3.9 febrile episodes per 100 days of hospitalization in adults with leukaemia. The overall risk for developing a febrile episode during a treatment-induced period of neutropenia varies between 30% and 80%, depending on the duration of neutropenia.[1] The extent and the duration of neutropenia are proportional to infectious complications. Empirical antibiotic therapy is often warranted, yet as a consequence of its use the cause of fever cannot be identified in the majority of the patients.[3] Approximately 60% of granulocytopenic patients will develop a lung infiltrate at some time during the course of the disease.[4,5] Besides infection, the most common causes of lung infiltrates in these patients are leukemic infiltration, congestive heart failure, hemorrhage, and drug toxicity.[6,7]

Since sputum is seldom being produced, many clinicians use bronchoscopy to establish the exact aetiology of the lung infiltrate. Several investigations have shown that bronchoalveolar lavage (BAL) is a valuable method in the diagnosis of pulmonary infections in the immunocompromised host.[8–12] The diagnostic yield of BAL has been found to vary between 15% and 60% in hematologic patients with lung infiltrates.[10,13–15] Combining different bronchoscopic techniques may increase the diagnostic yield.[16]

In immunocompromised patients BAL-fluid (BALF) may be contaminated by microbial flora from the upper airways, especially Gram-positive bacteria, yeasts and fungi. In order to reduce the oropharyngeal contamination during sampling, protected bronchoscopic techniques such as protected specimen brush (PSB) and protected bronchoalveolar lavage (PBAL) were developed. In ventilator-associated pneumonia these techniques seem to be of additive value, especially in those patients not receiving antibiotic treatment.[17]

This prospective study was designed to compare the diagnostic yield of the conventional BAL versus new techniques such as PSB and PBAL in patients with hematologic malignancies and lung infiltrates.

Methods

Patients

A prospective study was undertaken in patients admitted to the University Hospital Groningen with hematologic malignancies during a period of 24 months. After written informed consent was obtained, 65 patients with 70 episodes of pulmonary infiltrates were included in the study. None of them were mechanically ventilated.

The inclusion criteria for entering the study protocol were: (1) new intrapulmonary abnormalities on the chest radiograph(s) and/or new respiratory symptoms and signs; (2) fever or previous period of fever; (3) the presence of a hematologic malignancy; (4) neutropenia defined as a neutrophil count of <500 or $<1000/mm^3$ with predicted decline to $<500/mm^3$.

Patients were excluded from the study if: (1) the hemodynamic and/or respiratory condition was unstable; (2) the platelet count was $<15\times10^9/l$ despite platelet transfusion; (3) the pO_2 was <7.5 kPa despite supplemental O_2.

From all included patients recent ($\leqslant$24 h) chest radiographs, frontal and lateral view, were obtained. The extent of the radiographic abnormalities and the radiographic types were classified before the bronchoscopic procedure. Patients were alternately included in one of the two groups. Broncnoscopic procedures were carried out by two experienced respiratory physicians (W.B. and T.W.) according to the standard protocol.

Study protocol

All patients fasted for at least 8 h prior to bronchoscopy. Premedication consisted of codeine (30 mg) taken orally 2 h before bronchoscopy and subcutaneous atropine (0.25 mg) given 15 min before the procedure. Ten minutes before bronchoscopy 10 ml of lidocaine (4%) was nebulized at tidal volume breathing. Maximally 5 ml of lidocaine (1%) was applied to the nose, throat, and vocal cords. Intravenously administered midazolam (5 mg) was used as needed to achieve additional sedation. Patients with severe thrombocytopenia ($<20 \times 10^9$/l) received a pooled platelet transfusion just before the procedure. Supplemental oxygen (4–6 l/min) was administered during the procedure, while oxygen saturation and pulse rate were monitored by pulse oxymetry.

For the PSB–PBAL procedure two large channel bronchoscopes (Olympus BF 1T-20 or Olympus XT 20; Olympus, Paes, The Netherlands) were available. Several types of flexible bronchoscope (FB) were used to perform the conventional BAL procedure.

Bronchoscopic techniques

The FB was gently introduced via the nose or mouth. When using the protected techniques, lidocaine (2%, to a maximum of 2 ml) was instilled through the suction channel of the FB. During introduction and inspection, suction of bronchial secretion was avoided. If additional local anesthetic was required to control coughing, this was given and the bronchoscope then replaced. The FB was also replaced if the amount of bronchial secretion was a disturbing factor for optimal visualization; with the first FB all secretions were removed. Using the chest radiographs (frontal and lateral view) as guidance, the FB was advanced to the chosen segmental or subsegmental bronchus. Selection of the correct bronchial region could also be influenced by visible intrabronchial abnormalities such as purulent secretions or mucosal changes. PSB and PBAL were always performed in the same segmental or subsegmental bronchus.

Bronchoalveolar lavage

The tip of the FB was wedged into the segmental bronchus corresponding to the area of radiographic abnormality. BAL was then performed by sequentially instilling and suctioning 50 ml of normal saline four times. The first aliquot obtained was considered to be bronchial secretion. This specimen was therefore considered to be non-representative, because of potential contamination with oropharyngeal flora. The other BALF aliquots were pooled and further processed in both the microbiology and cytology laboratories.

Protected specimen brush

The PSB catheter (Microbiology Brush, Mill-Rose Laboratory Inc., OH, USA) was introduced into the selected segmental or subsegmental bronchus and advanced 3 cm out of the bronchoscope. The inner catheter was protruded to eject the distal wax plug into a large airway, and the catheter was advanced into the desired subsegment. If purulent secretion was visualized, the brush was rotated into them. In the absence of purulent secretions, the brush was advanced to a wedge position with gentle rotation. After specimen collection, the brush was retracted into the inner catheter, the inner catheter pulled back into the outer catheter, and the whole system removed. The distal parts of both inner and outer catheter were separately and consecutively wiped clean with 70% alcohol. The brush was then advanced and a small quantity of secretion was smeared onto two sterile microscope slides for additional staining. Subsequently, the brush was aseptically placed into a tube containing 2 ml of normal saline. The tube and one smear were immediately delivered to the microbiology laboratory. The other smear and the remaining part of the solution were used for cytological examination.

Protected bronchoalveolar lavage

After the removal of the PSB catheter from the bronchoscope, the PBAL catheter (Protected Bronchoalveolar Lavage Balloon Catheter, Mill-Rose Laboratory Inc., OH, USA) was introduced and advanced 2 cm into the selected segmental or subsegmental bronchus. The balloon was inflated with 2 ml of air for optimal occlusion of the bronchial lumen. The distal plug was ejected by

instilling 2 ml of sterile normal saline through the irrigation lumen. Subsequently, PBAL was performed by sequentially instilling and gently suctioning five 30 ml aliquots of normal saline at 37 °C. The balloon was deflated and the entire catheter was retracted. PBAL fluid obtained after the first aliquot was discarded. The remaining PBAL fluid was divided equally for microbial and cytological analyses.

Laboratory processing of specimens

Bronchoalveolar lavage

The BALF was vortexed for 60 s. From this suspension 0.05 ml was plated out on sheep blood agar, chocolate agar, McConkey 3 agar, and Saboraud's agar (Oxoid, Basingstoke, UK). All plates were incubated for maximally 4 days at 37 °C. Another 0.05 ml was inoculated onto a Brucella Blood Agar (BBA) plate and incubated anaerobically for 5 days. Semiquantitative cultures were performed according to generally accepted methods. The number of colony-forming units (cfu) was counted, with growth in the first quadrant only considered to be less than 10^4 cfu/ml. Growth into the second quadrant was defined as 10^4–10^5 cfu/ml, and into the third quadrant as more than 10^5 cfu/ml. Microorganisms were identified by standard methods.

Five hundred microlitres of BALF was suspended in GLY medium for viral culture. Twenty millilitres of suspension was centrifuged at 2000 rpm for 10 min. The supernatant was decanted, and the cell pellet was re-suspended in 2 ml of normal saline. If the specimen contained blood, the pellet was re-suspended in 10 ml of sterile H_2O at 4 °C in order to haemolyse the red blood cells. Subsequently, the same procedure of centrifugation and re-suspension with 2 ml of normal saline was performed. From this pellet slides were prepared for staining by Gram, Giemsa, toluidine-blue and calcofluor. From the re-suspended pellet cultures for *Legionella* sp. and mycobacteria were also performed.

BALF was sent for cytological analysis and was fixed in an equal volume of alcohol-polyethyleneglycol (50–2%). Smears obtained after centrifugation (1000 rpm for 10 min.) and cytocentrifuge preparation (Cytospin III, Shandon Southern Instruments, Sewickly, PA, USA) were stained by Papanicolaou, Grocott methenamine silver, auramine–rhodamine, and hematoxylin–eosin, examined for viral, fungal, and parasitic infections, and used for the detection of siderophages and malignant cells.

Protected specimen brush

The diluted PSB specimen (2 ml) was mechanically vortexed for 60 s. From this solution a Gram stain and a Ziehl–Neelsen stain was prepared. Two dilutions (0.1 and 0.001 ml) of the original specimen were plated out on different media (see BAL) for quantitative cultures. If growth occurred, colony counts were performed, and identification obtained for each microorganism. Five hundred microlitres of the initial dilution was diluted in 1 ml normal saline for Löwenstein culture for mycobacteria. If indicated, 0.2 ml was used for Legionella culture. Another 0.1 ml was inoculated in GLY medium for viral culture. Cytological analysis was similar to BAL.

Protected bronchoalveolar lavage

The microbiological and cytological analysis of PBAL was almost similar to the BAL analysis. From the original suspension of PBAL one 100-fold dilution was made. Aliquots of 0.1 ml each were plated onto the different media (see BAL). In contrast to BAL, quantitative cultures were performed.

Diagnostic criteria

The definite etiologies of the pulmonary infiltrates were established by combining the results of positive blood cultures, microbiological and cytological examination of the bronchoscopic samples, open lung biopsy, and/or outcome of autopsy. Probable etiologies were defined as the presence of characteristic abnormal radiographic signs (e.g. halo or air-crescent sign observed on CT-scan which is very suggestive for invasive pulmonary apsergillosis), isolation of a pathogen from sputum, abnormal serological test(s) such as complement fixation (respiratory pathogens), enzyme-linked immunosorbent assay (IgG to *Aspergillus fumigatus*, immunodiffusion (*A. fumigatus)*, and the result of antimicrobial treatment.

Detection of microorganisms that are not normally present in the oropharyngeal area, or the presence of malignant cells in one of the stains was considered to be a proven aetiology. In BAL, bacterial growth of $\geqslant 10^4$ cfu/ml from the original respiratory secretions was considered to be diagnostic. For PSB and PBAL samples the threshold for detection of a single pathogen was $\geqslant 10^3$ and $\geqslant 10^4$ cfu/ml of the original secretions, respectively.

Statistical analysis

All continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test for

normal distribution. The independent samples *T*-test was used for normally distributed variables and the χ^2-test for dichotomous variables. The software package SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A *P*-value of <0.05 was used to assess statistical significance of all tests.

Results

Clinical characteristics

Sixty-five patients with hematologic malignancies participated in the study and were subjected to 70 bronchoscopic procedures; 35 conventional BAL procedures and 35 protected techniques (PSB and PBAL) procedures. In seven cases the protected techniques were not well or not completely carried out. Therefore, the results of 35 conventional BAL procedures and 28 PSB and PBAL procedures were studied. Patient characteristics are summarized in Table 1. The majority of the patients had acute myeloid leukaemia as an underlying disease with severe granulocytopenia.

In both groups, alveolar consolidation was the predominant radiographic finding on the chest X-ray. Radiographic patterns extended to both lungs in more than half of the patients. In spite of progressive respiratory symptoms, no radiological abnormalities were detected in 4 patients of the PSB–PBAL group. Cavitation was observed only in the BAL group (3 cases); in one patient pulmonary aspergillosis was presumed to be the cause of cavitation.

Before bronchoscopy various schemes of antimicrobial treatment were used. Antibiotic treatment was started empirically in almost all patients at onset of fever. Due to the possibility of a fungal infection, amphotericin B was used in 10 patients of the BAL group, and 12 of the PSB–PBAL group, respectively. Only a small number of patients did not receive intravenous antimicrobial treatment. Most patients were also treated with an oral regimen for selective decontamination of the digestive tract.

Microbiological results

Causative pathogens were identified by bronchoscopic techniques in 17 (27%) of the 63 procedures (Table 2). In both groups *A. fumigatus* was the pathogen most frequently isolated, with no difference in diagnostic yield between the two techniques. Viruses were cultured from the BALF in 4 cases. Bacterial pathogens with growth above the defined detection threshold were cultured by PSB in 2 cases, by PBAL in 1 case and by BAL in none of the cases (Table 3). Leukemic cells were detected

Table 1 Patient characteristics in BAL group and PSB–PBAL group.

	BAL group	PSB–PBAL group
Patients (*n*)	32	26
Episodes with pulmonary infiltrates (*n*)*	35	28
Age (yrs)†	58 (21–74)	42 (19–73)
Acute myeloid leukemia (*n*)‡	19 (59%)	16 (62%)
Non-Hodgkin's lymphoma (*n*)	5 (16%)	2 (8%)
Hodgkin's lymphoma (*n*)	2 (6%)	5 (16%)
Burkitt's lymphoma (*n*)	3 (9%)	—
Other hematologic malignancies (*n*)§	3 (9%)	3 (9%)
Temperature (°C)‡,¶	39.0 (37.1–40.3)	39.1 (37.1–40.2)
Duration of fever (days)‡,¶	11 (0–55)	15 (0–55)
WBC (10^9/l)‡,¶	1.0 (0.1–34.7)	0.4 (0.1–27.7)
Hb (g/l)‡,¶	99 (71–128)	96 (76–129)
Platelet count (10^9/l)‡,¶	28 (1–340)	(24 (4–315)
Duration of neutropenia (days)‡,¶	27 (0–489)	30 (0–380)

*Some patients had more than one episode of pneumonia.
†Median (range), $P = 0.01$.
‡Statistically not significant.
§BAL group: myelodysplastic syndrome, acute lymphoblastic leukemia, and refractory = anaemia with an excess of blasts in transformation; PSB–PBAL group: hairy cell leukemia, acute lymphoblastic leukemia, and aplastic anaemia.
¶Median (range), before bronchoscopy.

Table 2 Microorganisms isolated.

	BAL ($n = 35$)	PSB ($n = 28$)	PBAL ($n = 28$)	PSB+PBAL ($n = 28$)
Aspergillus fumigatus	2	2*	2*	4
A. fumigatus+Mucor sp.	1	—	—	—
A.fumigatus+Herpes simplex virus	1	—	—	—
Mycobacterium tuberculosis	1†	—	1†	1
Pneumocystis jerovicii	1	1	—	1
Respiratory syncytial virus	1	—	—	—
Parainfluenzae 3 virus	1	—	—	—
Cytomegalovirus	1	—	—	—
Coagulase-negative staphylococci (cfu/ml)	—	1 (5×10^3)	—	1
Lactobacillus sp. (cfu/ml)+HSV	—	—	1 (1×10^4)	1
Diagnostic yield‡	9 (26%)§	4 (14%)	4 (14%)	8 (29%)

*The two patients in whom *A. fumigatus* was detected by PSB are not the same two patients in whom it was detected by PBAL.
†Probably false positive result of acid-fast staining. Mycobacterial cultures were negative.
‡No statistical difference between BAL group and PSB–PBAL group.
§In two patients leukemic cells were demonstrated in BALF.

Table 3 The growth density of isolated bacteria by BAL, PSB, and PBAL.

Growth	BAL ($n = 35$)	PSB ($n = 28$)	PBAL ($n = 28$)
	No. bacteria*		
10^5 cfu/ml	0	0	0
10^4 cfu/ml	2†	0	
	1‡		
10^3 cfu/ml	—	1‡	3†,§
$<10^3$ cfu/ml¶	13	6	11
No growth**	14	20	13

*Specimens yielding multiple bacteria consistent with oropharyngeal flora were considered to be unrepresentative specimens and are therefore excluded from the table.
†Coagulase negative staphylococci, considered contaminants.
‡*Lactobacillus* sp. (see also Table 4).
§*E. coli*.
¶Including *C. albicans* (BAL: 5, PSB: 1, PBAL: 1).
**Additiontional stains were also negative.

in BALF in two patients; however, contamination with blood could not be excluded.

The overall diagnostic yield was 26% with conventional BAL procedure and 14% each with PSB and PBAL (Table 2). By combining both protected techniques the diagnostic yield increased to 29%. The aetiology of pneumonia was detected by blood cultures in five patients (Table 4). In these patients bronchoscopic specimens were negative; one of the pathogens was detected in BALF in a growth density of $<10^3$ cfu/ml (Table 3).

Combining all diagnostic tests such as microbiological and serological tests, radiography, and histological examinations (including post-mortem) a definite diagnosis was made in 40% and 64% of cases of the BAL group and the PSB–PBAL group, respectively (Table 4). Pulmonary aspergillosis especially was underdiagnosed in both groups; only 4 of 15 (27%) cases were detected by invasive bronchoscopic techniques. Probable invasive aspergillosis was diagnosed by bronchoscopy in 6 patients, bronchoscopy and computed tomography (CT) scanning in 1 patient, CT scanning and Magnetic Resonance Imaging in 5 patients, and serology in 1 patient. The remaining 2 patients were diagnosed as proven invasive aspergillosis by histology. Treatment was adapted to the results in those patients with *P. carinii* and *A. fumigatus* infections in 8 patients.

Table 4 Presumptive aetiology of pulmonary infiltrates based on microbial, radiological, and pathological (including post-mortem) examinations.

Aetiology	BAL group ($n = 35$)	PSB–PBAL group ($n = 28$)
Definite *Aspergillus pneumonia*	1	1
Probable *Aspergillus pneumonia*	4*	9†
C. albicans pneumonia	—	1‡
Viral pneumonia	3	2§
P. jerovicii pneumonia	1	1
Bacterial pneumonia	3¶	1**
Drug-induced infiltrate	1	1
Tumor infiltrate	1	2
Total	14 (40%)	18 (64%)
Unknown	20 (60%)	12 (36%)

*Co-infection with Herpes simplex virus.
†Co-infection with *Lactobacillus* spp.
‡Positive blood culture.
§Positive serology.
¶*S. pneumoniae*, *S. aureus*, and α-hemolytic streptococcus (positive blood culture).
**Coagulase-negative staphylococcus (positive blood culture).

Assessment and complications of the invasive procedures

The majority of the patients had an oxygen desaturation (<90%) during the bronchoscopic procedure. Severe coughing was a frequently recorded symptom. PSB caused no severe bleeding; none of the patients needed a transfusion with platelets directly after bronchoscopy. Coughing and bleeding caused by PSB procedure resulted in a more complex positioning of the PBAL catheter. Partial luxation of the balloon of the PBAL catheter by coughing, leading to leakage of the PBAL fluid, was regularly observed.

The recovery of the instilled fluid (150 ml) by PBAL catheter was disappointing; in most patients the recovered volume of PBAL fluid was less than 10 ml. No pneumothorax, severe bleeding or other complications were observed in any of 63 bronchoscopic procedures. One patient died within 24 h after bronchoscopy due to fulminant *P. carinii* pneumonia.

Discussion

Invasive techniques such as bronchoscopy are often used for the identification of the causative pathogen(s) in immunocompromised patients. Various bronchoscopic techniques, such as BAL, PSB and PBAL, have been used in patients with hematologic diseases and were compared in this study. The sensitivity of BAL to diagnose the cause of pulmonary infiltrates in these patients from 15% to 66%.[13,14,16,18,19]

In the present study, the diagnostic yield of BAL (26%) was superior to PSB (14%) and PBAL (14%) individually, however the results of the combination of both protected procedures was almost identical to that of BAL. In other studies, the combination strategy was superior to the individual methods.[22,23] The higher diagnostic yield reported, compared to the present study, may be explained by two factors. First, the patient groups reported were different from those in the present study; most non-granulocytopenic patients had AIDS or were transplant recipients.[20,21,24] Secondly, the rate of patients that did not received antimicrobial treatment before bronchoscopy was lower in the other studies, whereas the duration of antibiotic pretreatment was shorter.

In another study the diagnostic yield of all endoscopic procedures (BAL, telescoping plugged catheter, PSB) was 53% in the granulocytopenic group and 61% in the non-granulocytopenic group.[15] Differences in underlying diseases, i.e. acute leukaemia type, and duration of antimicrobial treatment, may be reasons for the relatively high diagnostic yield.

This was illustrated by Ewig[25] studying patients with hematologic malignancies and pulmonary complications in the ICU. Pathogens were retrieved by BAL in 31% and PSB in 20% of the patients, whereas blood cultures and tracheobronchial aspirate revealed a positive result in 30% and 6%, respectively. In only 37 (42%) cases infectious aetiology was diagnosed during patient's lifetime or at necropsy. Remarkable was the low percentage of infection with *Aspergillus* spp. (3 cases).

The clinical significance of culture results just under the threshold level, especially during an antibiotic regimen, is unclear. Data obtained from patients with ventilator-associated pneumonia suggest borderline results should be carefully interpreted. It might imply that bronchoscopy should be repeated if clinical suspicion is adequately high.[26,27] The results of quantitative cultures in the present study indicate that contamination also occurred with the protected techniques.

Invasive aspergillosis is often seen in granulocytopenic patients and bone marrow transplantation recipients.[28] Mortality in these high-risk groups may approach 90%. Much of this high mortality may reflect the difficulty in establishing a correct diagnosis in an early stage. BAL analysis by Kahn et al.[29] demonstrated invasive pulmonary aspergillosis in 9 of the 17 (53%) immunocompromised patients; in patients without aspergillosis BAL had a specificity of 92%. The low sensitivity was confirmed by others,[30,31] whereas the values of the specificity were conflicting. PSB, as shown in our results and as also found by others, provides a low diagnostic yield of invasive aspergillosis.[30]

Other methods, such as CT scanning and galactomannan-based antigen detection diagnosing pulmonary aspergillosis, may be complementary. CT features considered consistent with angioinvasive aspergillosis are the halo sign and air-crescent sign.[32] In the present study, CT scanning diagnosed approximately half of the patients with probable aspergillosis. Moreover, a CT scan might serve as guidance for the optimal timing, type and site of the biopsy.

The diagnostic accuracy of chest radiograph in the evaluation of acute pulmonary complications in granulocytopenic patients is generally low.[4] As shown in our study the radiographic presentation (often alveolar consolidation) is neither typical nor specific for any of the diagnoses (e.g. hemorrhage, infection, tumor infiltration, etc.) nor typical for a specific pathogen. A recent study indicated that chest CT scanning provides more specific information in the immunocompromised host.[33]

If all diagnostic examinations remain negative, tissue examination should be considered and can be of additive value.[21] However, bronchoscopic biopsy procedures are often contraindicated because of the presence of coagulopathies. In our study, with transfusion of platelets before the bronchoscopic procedure, no severe bleeding was observed. Bronchoscopy in bone marrow transplantation recipients led to 18% minor complications (desaturation, minor bleeding, hypotension, and stridor) and 8% major complications (severe bleeding, requirement for mechanical ventilation, and death).[34] In our study bleeding initiated by PSB sometimes partially obstructed the lumen of the PBAL catheter leading to a lower BALF recovery. Therefore, video-assisted thoracoscopic surgery or open lung biopsy are often performed and may provide a more specific diagnosis compared to BAL.[35]

This study illustrates that the application of modern techniques does not necessarily improve diagnostic results. In this group of hematologic patients with granulocytopenia and pulmonary infiltrates, the diagnostic value of all bronchoscopic techniques during antibiotic treatment was low. No difference in diagnostic yield was found between PSB–PBAL and BAL. Especially in this group of patients the combination of PSB and PBAL, although safe, required more skills and effort from the bronchoscopist. Although we did not time the duration of the procedures, they might require more time than the conventional BAL, which would conceivably impact on discomfort experienced by patients. If appropriate imaging like early chest CT is combined with an appropriate bronchoscopic diagnostic technique such as BAL, we expect that the diagnostic yield will be improved. Further studies are needed to evaluate this.

References

1. Young LS. Management of infections in leukemia and lymphoma. In: Rubin HR, Young LS, editors. *Clinical approach to infection in the compromised host*. New York and London: Plenum Medical Book Company; 1988. p. 467–501.
2. Boggs DR, Friedland GH. Clinical studies of fever and infection in cancer. *Cancer* 1960;**13**:1240–53.
3. Pizzo PA. Evaluation of fever in the patient with cancer. *Eur J Cancer Clin Oncol* 1989;**25**(suppl 2):S9–S16.
4. Tenholder MF, Hooper RG. Pulmonary infiltrates in leukemia. *Chest* 1980;**78**:468–73.
5. Novakova IR, Donnelly JP, De Pauw B. Potential sites of infection that develop in febrile granulocytopenic patients. *Leuk Lymphoma* 1993;**10**:461–7.
6. Rosenow EC, Wilson WR, Cockerill FR. Pulmonary disease in the immunocompromised host (first of two parts). *Mayo Clin Proc* 1985;**60**:473–87.
7. Quabeck K. The lung as a critical organ in marrow transplantation. *Bone Marrow Transplant* 1994;**14**(Suppl 4): S19–28.
8. Baughman RP. Use of bronchoscopy in the diagnosis of infection in the immunocompromised host. *Thorax* 1994;**49**: 3–7.
9. Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. *Ann Intern Med* 1984;**101**:1–7.
10. Kahn FW, Jones MJ. Analysis of bronchoalveolar lavage specimens from immunocompromised patients with a protocol applicable in the microbiology laboratory. *J Clin Microbiol* 1988;**26**:1150–5.

11. Springmeyer SC, Hackman RC, Holle R, Geoffrey M, Greenberg M, Weems CE, et al. Use of bronchoalveolar lavage to diagnose acute diffuse pneumonia in the immunocompromised host. *J Infect Dis* 1986;**154**:604–10.
12. Martin WJ, Smith TF, Sanderson DR, Brutinel WM, Cockerill FR, Douglas WW. Role of bronchoalveolar lavage in the assessment of opportunistic pulmonary infections: utility and complications. *Mayo Clin Proc* 1987;**62**:549–57.
13. Saito H, Anaissie EJ, Morice RC, et al. Bronchoalveolar lavage in the diagnosis of pulmonary infiltrates in patients with acute leukemia. *Chest* 1988;**94**:745–9.
14. Marra R, Pajano L, Pagliari G, Frigieri L, Storti S, Morace G, et al. The yield of bronchoalveolar lavage in the etiological diagnosis of pneumonia in leukemia and lymphoma patients. *Eur J Haematol* 1993;**51**:256–8.
15. Cordonnier C, Escudier E, Verra F, Brochard L, Bernaudin JF, Fleury Feith J. Bronchoalveolar lavage during granulocytopenic episodes: diagnostic yield and cellular pattern. *Eur Respir J* 1994;**7**:114–20.
16. Von Eiff M, Zühlsdorf M, Roos N, Thomas M, Büchner T, van de Loo J. Pulmonary infiltrates in patients with haematologic malignancies: clinical usefulness of non-invasive bronchoscopic procedures. *Eur J Haematol* 1995;**54**:157–62.
17. Chastre J, Trouillet JL, Fagon JY. Diagnosis of pulmonary infections in mechanically ventilated patients. *Sem Respir Infect* 1996;**11**:65–76.
18. Maschmeyer G, Link H, Hiddemann W, Meyer P, Helmerink M, Eisenmann E, et al. Pulmonary infiltrations in febrile patients with neutropenia. Risk factors and outcome under empirical antimicrobial therapy in a randomized multicenter study. *Cancer* 1994;**73**:2296–304.
19. Lindhart Pedersen T, Pedersen M, Myhre J, Milman N, Johnsen H. Bronchoalveolar lavage is a safe and informative procedure in haematologic patients with nonresolving pneumonia. *Eur J Haematol* 1992;**49**:280–1.
20. Rano A, Agusti C, Jimenez P, Angrill J, Benito N, Danes C, et al. Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures. *Thorax* 2001;**56**:379–87.
21. Jain P, Sandur S, Meli Y, Arroliga AC, Stoller JK, Mehta AC. Role of flexible bronchoscopy in immunocompromised patients with lung infiltrates. *Chest* 2004;**125**:712–22.
22. Jolis R, Costella J, Puzo C, Coll P, Abeledo C. Diagnostic value of protected BAL in diagnosing pulmonary infections in immunocompromised patients. *Chest* 1996;**109**:601–7.
23. Xaubet A, Torres A, Marco F, Puig-De la Bellacasa J, Faus R, Agusti-Vidal A. Pulmonary infiltrates in immunocompromised patients. Diagnostic value of telescoping plugged catheter and bronchoalveolar lavage. *Chest* 1989; **95**:130–5.
24. Sauleda J, Maimo A, Riera M, Ramirez J, Togores B, Pons S, et al. A new bronchoscopic technique for the diagnosis of bacterial pneumonia in HIV-positive patients. *Respir Med* 1997;**91**:530–6.
25. Ewig S. Pulmonary complications in patients with haematological malignancies treated at a respiratory ICU. *Eur Respir J* 1998;**12**:116–22.
26. Baker AM, Bowton DL, Haponik EF. Decision making in nosocomial pneumonia. An analytic approach to the interpretation of quantitative bronchoscopic cultures. *Chest* 1995;**107**:85–95.
27. Dreyfuss D, Mier L, Le Bourdelles G, Djedaini K, Brun P, Boussougant Y, et al. Clinical significance of borderline quantitative protected brush specimen culture results. *Am Rev Respir Dis* 1993;**147**:946–51.
28. Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis* 1996;**23**:608–15.
29. Kahn FW, Jones JM, England DM. The role of bronchoalveolar lavage in the diagnosis of invasive pulmonary aspergillosis. *Am J Clin Pathol* 1986;**86**:518–23.
30. Von Eiff M, Roos N, Fegeler W, Von Eiff C, Zühlsdorf M, Glaser J, et al. Pulmonary fungal infections in immunocompromised patients: incidence and risk factors. *Mycoses* 1994;**37**: 329–35.
31. Pisani RJ, Wright AJ. Clinical utility of bronchoalveolar lavage in immunocompromised hosts. *Mayo Clin Proc* 1992; **67**:221–7.
32. Brown MJ, Worthy SA, Flint JD, Müller NL. Invasive aspergillosis in the immunocompromised host: utility of computed tomography and bronchoalveolar lavage. *Clin Radiol* 1998;**53**:255–7.
33. Caillot D, Casasnovas O, Bernard A, Couaillier JF, Durand C, Cuisenier B, et al. Improved management of invasive pulmonary aspergillosis in granulocytopenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997;**15**:139–47.
34. Dunagan DP, Baker AM, Hurd DD, Haponik EF. Bronchoscopic evaluation of pulmonary infiltrates following bone marrow transplantation. *Chest* 1997;**111**:135–41.
35. Ellis ME, Spence D, Bouchama A, Antonius J, Bazrbashi M, Khougeer F, et al. Open lung biopsy provides a higher and more specific diagnostic yield compared to bronchoalveolar lavage in immunocompromised patients. *Scand J Infect Dis* 1995;**27**:157–62.