Original Article

Pulmonary infections in patients with and without hematological malignancies: diagnostic yield and safety of flexible bronchoscopy—a retrospective analysis

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Background: Fiberoptic bronchoscopy (FOB) with broncho-alveolar lavage (BAL) is frequently performed in patients with hematological malignancies and pulmonary opacities. While the safety of the procedure in this patient population has been shown, data about the diagnostic yield widely differ between studies. Furthermore, data comparing diagnostic yield and safety of flexible bronchoscopy to narrow sources of pulmonary infections in patients with and without underlying hematological malignancy are lacking.

Methods: We carried out a retrospective analysis of bronchoscopies done for the diagnostic work-up of pulmonary infections. Diagnostic yield and the occurrence of complications in patients with and without hematological disease were compared.

Results: In total n=268 bronchoscopies were done in patients suffering from a hematological malignancy (HM) compared to n=408 bronchoscopies in patients without hematological malignancy (NHM). The overall diagnostic yield was similar and did not differ between the groups (HM: 67.2% *vs.* NHM: 64.7%; P=0.5622). However, when cultures positive for Candida were not considered as clinically relevant diagnostic yield was higher in the HM group (HM: 62.7% *vs.* NHM: 53.9%; P=0.0261) due to a higher detection rate of fungi and viruses (both P<0.001). Interestingly, the diagnostic yield for bacteria was not decreased by pre-treatment with antibiotics in either group (both P>0.05). There was no difference in the complication rate between the groups and most complications were considered as minor.

Conclusions: In summary, our data demonstrate similar diagnostic yield and safety of flexible bronchoscopy for diagnosing pulmonary infection in patients with and without underlying hematological malignancy.

Keywords: Bronchoscopy; broncho-alveolar lavage (BAL); pulmonary infections; hematological malignancy

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Introduction

Respiratory complications such as pulmonary infections frequently occur in patients suffering from hematological malignancies. Causes for respiratory complications, apart from opportunistic infections include chemo- or radiotherapy induced lung toxicity, invasion by malignant cells, graft-versus-host-disease, and increasingly immunological side effects such as pneumonitis due to the incremental availability of immune based therapies for this patient group. Risk factors for respiratory complications include underlying pulmonary diseases and active smoking (1,2).

Fiberoptic bronchoscopy (FOB) with broncho-alveolar lavage (BAL) is commonly performed in hematological patients with pulmonary opacities and suspected pulmonary infection. In general, BAL is thought to provide valuable diagnostic information and an acceptable safety profile for FOB in this patient population has been demonstrated although a recent study found an association of FOB with increased hospital mortality in immunocompromised patients suffering from respiratory failure (3,4). The diagnostic yield for the identification of infectious agents by FOB with BAL shows a considerable variation within different studies as broad-spectrum antibiotics are routinely administered before the initiation of FOB in patients with suspected pulmonary infections and hematologic malignancies (3,5-7). In addition, most studies investigating the diagnostic outcome of FOB with BAL included only a small number of patients and so far, no data are available comparing diagnostic yield and safety of FOB for suspected pulmonary infection in patients with and without hematological disease. Hence, the aim of this retrospective analysis was to analyze safety and diagnostic yield of FOB for the diagnosis of pulmonary infections in two large patient cohorts with (HM) and without underlying hematological malignancy (NHM).

Methods

Data analysis was done with regard to the Declaration of Helsinki (as revised in 2013). The Institutional Ethical Review Board for Human Studies at RWTH ("Rheinisch-Westfälische Technische Hochschule") University was involved and confirmed that a formal approval was not required as this retrospective analysis required neither an intervention nor irregularity of privacy or anonymity (EK 099/17). Individual patient consent was waived by the Review Board due to the observational nature of the study.

An analysis of all flexible bronchoscopies for the evaluation of suspected pulmonary infection between January 2013 and December 2017 performed at the department of Pneumology at the University Hospital RWTH Aachen was conducted. The indication for bronchoscopy in aplastic patients with underlying hematological malignancies in general followed the recommendations of the German Infectious Disease Working Party (AGIHO) of the German Association for Hematology and Oncology (DGHO) (8-10). Briefly, CT scans are performed early in the disease process and if these reveal signs of infection/infiltration bronchoscopy/BAL are performed if the patient's general condition allows so. In patients who are not aplastic the indication for bronchoscopy is made individually based on the clinical history, laboratory findings and imaging (typically CT scans).

Bronchoscopies of patients with critical illnesses (e.g., patients with acute respiratory failure or patients needing vasopressor support) were performed on intensive care or intermediate care wards and were not included in the analysis. All bronchoscopies were performed by board-certified specialists in pulmonary or internal medicine experienced in bronchoscopy or under their direct supervision. All physicians performing bronchoscopy were trained and experienced in airway management (endotracheal intubation by direct laryngoscopy and by FOB), as well as in the management of acute emergency situations (e.g., shock, cardiac arrhythmias, or acute respiratory failure) and critical care medicine. In case of complications a second physician experienced in bronchoscopy, as well as an emergency team from the ICU were available on short notice. Standard monitoring included electrocardiogram, oxygen saturation (SpO_2), and non-invasive blood pressure (NIBP).

To increase patient tolerance and cooperation patients were sedated during the procedure typically by a combination of midazolam, fentanyl and propofol. In addition, lidocaine was administered topically to the vocal cords and the bronchial system. Bronchoalveolar lavage was performed using flexible bronchoscopes (Olympus, Japan). The bronchoscope was wedged into a segment where lung infiltration was present, or the infiltration was most severe. A total of 100 mL sterile saline solution was instilled in aliquots of 20 mL and the fluid was recovered by gentle aspiration. Original data was retrieved from an electronic patient record system (medico, Siemens, Germany) as well as from paper-based medical records and was collected in

a Microsoft Access database (Microsoft, Redmond, USA), as described previously (11,12). Demographic (age, sex) and epidemiological data (e.g., cardio-vascular or chronic pulmonary co-morbidities) were recorded, as well as data about underlying hematological malignancies, any form of immunosuppression, the amount of administered sedative drugs (midazolam, fentanyl and propofol) and the occurrence of complications during the procedure as documented by the investigator. The following patient groups without hematological malignancy were considered as immunocompromised: patients with a non-hematological malignancy who had received cytostatic chemotherapy within 30 days, solid organ transplant recipients, HIV patients with AIDS-defining illness, patients with corticosteroid-therapy with at least 10 mg prednisone equivalent for more than 30 days or other immunosuppressive drugs (e.g., methotrexate, azathioprine, cyclosporine), pre-defined immune deficiency syndromes, and non-malignant hematological disorders with neutropenia defined as a neutrophil count below 500/µL.

Complications were categorized as adverse events (AEs) and severe adverse events (SAEs) as previously described (11,12). Briefly, SAEs were defined as death within 24 h after bronchoscopy, pneumothorax, severe bleeding (defined as necessity for intubation or placement of a bronchus blocker), need for post-interventional ventilation, epileptic seizure or any event leading to an intensive or intermediate care unit admission after the procedure. AEs were defined as any event judged as complication in the bronchoscopy report not fulfilling the definition of a severe AE, e.g., transient respiratory deterioration, short time mechanical ventilation during the procedure, hypotension, prolonged recovery after bronchoscopy as judged by the bronchoscopist, or minor bleedings.

Patient records were also screened for the results of microbiological tests in samples obtained during the procedure, e.g., bacterial or fungal cultures, aspergillus antigen detection, or molecular detection of respiratory viruses. In accordance with previous studies, the microbiological yield was defined as the percentage of procedures in which a microbiological agent could be identified (6).

Statistical analysis

Statistical analysis was performed using GraphPadPrism (GraphPad Software, La Jolla, USA). Unless otherwise stated, all data are presented as mean ± standard deviation (SD) after testing for normal distribution (Kolmogorov-Smirnov test). A two-group comparison was performed using the unpaired *t*-test for normally distributed data or the Mann-Whitney test for non-normally distributed data. The Fisher's exact test was used for categorical data. Statistical significance was defined as a P value <0.05.

Results

Patient characteristics

In the observed time period n=268 bronchoscopies for the evaluation of suspected pulmonary infection were performed in 201 HM patients, whereas n=408 bronchoscopies for the evaluation of suspected pulmonary infection were done in 371 NHM patients. Patient characteristics are summarized in *Table 1*. Compared to NHM patients HM patients were older (NHM: 57.5±18.0 *vs.* HM: 62.9±14.4 years; Δ 5.4±1.5 years; 95% CI, 2.5 to 8.3; P=0.0003) and had a lower prevalence of chronic lung diseases (NHM: 44.2% *vs.* HM: 26.9%; P<0.0001). Apart from that there were no significant differences between the groups.

At the time of bronchoscopy 39.2% of the HM group patients were neutropenic defined as a neutrophil count below 500/µL, and 49.3% of the patients had a platelet count of 50/nL or below.

Microbiological yield

Details concerning microbiological yield are listed in *Table 2*, microorganisms which were frequently detected in samples obtained by bronchoscopy can be found in *Table 3*. The overall microbiological yield (any bacteria, fungi or viruses) did not differ between the two patient groups (HM: 67.2% *vs.* NHM: 64.7%; P=0.5622). However, when cultures positive for Candida were not considered as clinically relevant the microbiological yield was significantly higher in the HM group (HM: 62.7% *vs.* NHM: 53.9%; P=0.0261). This difference in diagnostic yield was due to a higher detection rate of fungi (HM: 23.1% *vs.* NHM: 9.8%; P<0.0001) and viruses (HM: 20.2% *vs.* NHM: 8.8%; P<0.0001) in the HM group whereas no differences were observed in the microbiological yield for bacteria (HM: 42.5% *vs.* NHM: 46.5%; P=0.3420).

In the NHM group n=131 procedures (32.1%) were performed in immunocompromised patients as defined in the material and methods section. Overall diagnostic yield (any bacteria, fungi apart from Candida or viruses) in these

Table 1 Patient characteristics

Variables	HM (n=201)	NHM (n=371)	P
Male, n (%)	127 (63.2%)	262 (70.6%)	0.0748*
Age, years	62.9±14.4	57.5±18.0	0.0003#
Weight, kg	75.3±14.5[1]	72.5±17.2[2]	0.0648#
Size, cm	172.4±9.9[3]	172.3±10.0[4]	0.9149#
FEV1, % predicted	84.3±22.1[5]	69.4±23.1[6]	<0.0001#
Cardio-vascular disease, n (%)	80 (39.8%)	148 (39.9%)	>0.9999*
Chronic pulmonary disease, n (%)	54 (26.9%)	164 (44.2%)	<0.0001*
Type of hematological malignancy[7]			
Acute myeloid leukemia	88 (43.8%)	NA	
Non-Hodgkin's lymphoma	73 (36.3%)	NA	
Acute lymphoblastic leukemia	13 (6.5%)	NA	
Chronic lymphoblastic leukemia	10 (5.0%)	NA	
Other	27 (13.4%)	NA	
Stem cell transplantation	49 (24.4%)	NA	

Data are mean ± standard deviation or number of patients (%). *, Fisher's exact test; #, student's *t*-test; [1], data were available for 191 out of 201 patients; [2], data were available for 325 out of 371 patients; [3], data were available for 196 out of 201 patients; [4], data were available for 343 out of 371 patients; [5], data were available for 131 out of 201 patients; [6], data were available for 178 out of 371 patients; [7], 10 patients were suffering from more than one hematological malignancy. HM, hematological malignancy; NHM, no hematological malignancy; FEV1, force expiratory volume in 1 s.

procedures was very similar compared to the HM group (HM: 62.7% *vs.* immunocompromised NHM: 62.6%; P>0.9999).

Interestingly, diagnostic yield for bacteria was similar in patients treated or not treated with antibiotics in both the HM (antibiotics: 45.4% *vs.* no antibiotics: 45.5%; P>0.9999) and the NHM group (antibiotics: 42.3% *vs.* no antibiotics: 46.0%; P=0.5730).

In the HM group clinical management was modified (e.g., change of the antimicrobial regime or exclusion of pulmonary infection) in 36.9% of the cases due bronchoscopy results.

Sedation during bronchoscopy

Bronchoscopies in both groups were mostly performed under combined sedation. Most procedures were done using a combination of midazolam, fentanyl and propofol (HM: 63.1% *vs.* NHM: 61.0%), followed by a combination of midazolam and fentanyl (HM: 17.9% *vs.* NHM: 17.9%) and by a combination of midazolam and propofol (HM: 14.2% *vs.* NHM: 11.8%). There were no significant differences in terms of sedation regimens between the groups (P=0.1739).

Complications

Details of AEs and SAEs are listed in *Table 4*. In general, occurrence of AEs was comparable between the two groups (HM: 14.2% *vs.* NHM: 15.7%; P=0.6580) and mostly comprised transient respiratory deterioration, difficulties to adequately sedate patients and minor bleedings. The rate of minor bleedings during the procedure did not differ between hematological patients with or without thrombocytopenia (2.3% *vs.* 2.2%). In addition, SAEs rarely occurred and there were no differences in the occurrence of SAEs between the groups (HM: 2.2% *vs.* NHM: 1.7%; P=0.7766).

Discussion

This study compared diagnostic yield and safety of FOB for the diagnostic work-up of suspected pulmonary infections

Table 2 Microbiological yield

Microbiological yield for	HM (n=268)	NHM (n=408)	P
Any agent	67.2%	64.7%	0.5622*
Any agent apart from Candida	62.7%	53.9%	0.0261*
Bacteria	42.5%	46.5%	0.3420*
Fungi	40.7%	33.1%	0.0495*
Fungi apart from Candida	23.1%	9.8%	<0.0001*
Viruses	20.2%	8.8%	<0.0001*

*, Fisher's exact test.

Table 3 Microorganisms detected in samples obtained by bronchoscopy

Type of microorganism	HM	NHM
Bacteria		
Enterobacteriaceae[1]	28 (10.4%)	55 (13.5%)
S. aureus	11 (4.1%)	31 (7.7%)
P. aeruginosa	5 (1.9)	14 (3.4)
Enterococcus spp.	19 (7.1%)	9 (2.2%)
Haemophilus spp.	12 (4.5%)	35 (8.6%)
M. tuberculosis	0 (0%)	23 (5.6%)
Fungi		
Candida spp.	63 (23.5%)	104 (25.5%)
Aspergillus spp.	29 (10.8%)	9 (2.2%)
P. jirovecii	34 (12.7%)	21 (5.1%)
Viruses		
Herpes simplex	27 (10.1%)	10 (2.5%)
Cytomegalovirus	20 (7.5%)	15 (3.7%)
Rhinovirus	8 (3.0%)	8 (2.0%)
Influenza virus	6 (2,2%)	4 (1.0%)

Data are number of positive tests (%). [1], *E. coli*, *Proteus*, *Klebsiella*, *Enterobacter*, *Serratia*, *Citrobacter*, *Hafnia*, *Morganella*.

in patients with and without underlying hematological malignancies. The overall microbiological yield was more than 60% in both groups which is in accordance with the highest results published so far (3,5-7,13).

Previous studies demonstrated a considerable variability for the diagnostic yield of FOB with BAL for the identification of microbiological pathogens in hematological patients which is in the range of 26% and 65% (3,5-7,13). Factors influencing diagnostic yield and contributing to this variability include differences in empirical antimicrobial regimens, in patient populations and in the availability of methods for the detection of different pathogens, e.g., culture techniques, assays for the detection of microbiological antigens, or PCR-based techniques (6,7).

Candida spp. are frequently isolated from the respiratory tract. They are mostly considered to be irrelevant as pneumonia related to Candida is an extremely rare event even in patients with hematologic malignancies (14).

Table 4 Complications

Type of complication	HM (n=268)	NHM (n=408)	P
AEs	58 (14.2%)	42 (15.7%)	0.6580*
Transient respiratory deterioration	20 (7.5%)	28 (6.9%)	0.7619*
Difficult to sedate	14 (5.2%)	19 (4.7%)	0.7200*
Minor bleedings	6 (2.2%)	9 (2.2%)	>0.9999*
Interruption of the procedure	3 (1.1%)	3 (0.7%)	0.6850*
SAEs	6 (2.2%)	7 (1.7%)	0.7766*
Pneumothorax	1 (0.4%)	4 (1.0%)	0.6532*
ICU/IMC admission	5 (1.9%)	3 (0.7%)	0.2756*
Severe bleeding	1 (0.4%)	0 (0.0%)	0.3964*

Data are number of procedures with complications (%). *, Fisher's exact test. AE, adverse event; SAE, severe adverse event; ICU, intensive care unit; IMC, intermediate care unit.

Hence the microbiological yield was also calculated omitting cultures only positive for Candida which resulted in a higher diagnostic yield of 62.7% in the HM group compared to 53.9% in the NHM group due to a higher proportion of tests positive for viruses and fungi as expected in this patient population. Still, microorganisms apart from *Candida* found in respiratory samples are not necessarily of clinical relevance which is supported by the finding that bronchoscopy results lead to a change in clinical management of hematological patients in 36.9% whereas the microbiological yield was 62.7%. The microbiological yield in procedures with immunocompromised patients of the NHM group was similar compared to the HM group. Consecutively, though the heterogeneity of immunocompromised non-hematological patients has to be taken into account, the presence of immunosuppression might be one possible explanation for the differences in diagnostic yield between the HM and the NHM group and emphasizes the role for FOB in diagnosing pulmonary infection especially in the context of immunosuppression.

Broad spectrum empiric antibiotic therapy should be initiated as early as possible in patients with hematological disorders when pulmonary infection is suspected especially in the context of neutropenia (15). On the other hand, this approach might decrease the microbiological yield of FOB with BAL. However, such an effect was not seen in our patient population which is in line with the results of a previous study whereas the influence of bronchoscopy results on patients' clinical management was even more pronounced than in the study done by Pagano and colleagues (3,6). Consecutively, in an appropriate clinical setting bronchoscopy can provide useful information even under concurrent antimicrobial therapy.

Apart from diagnostic yield safety aspects also must be considered when performing an invasive procedure such as flexible bronchoscopy. Overall, the occurrence of complications in our study did not differ between the two groups, most complications resolved by the end of the bronchoscopy, and severe complications were rare. In the literature highly variable complication rates for flexible bronchoscopy in the management of pulmonary opacities are reported due to a lack of standardization in the documentation of complications (7). The most frequent complications in both groups were transient respiratory deterioration or problems related to sedation. Though a considerable percentage of patients in the HM group had a low platelet count, bleedings rarely occurred in both groups and most bleedings were considered as minor. Similar observations have been made previously by Nandagopal *et al.* who demonstrated that FOB with BAL can be safely performed in patients with thrombocytopenia (16). Taken together in accordance with most studies our results showed a favorable safety profile of flexible bronchoscopy in hematological patients (3,5). Nevertheless, the potential clinical benefit of the results obtained by bronchoscopy should always be balanced against the risks of the procedure especially in patients with respiratory failure (4).

This analysis has several limitations which need to be addressed. Firstly, the data were not obtained prospectively. Therefore, bronchoscopies and the diagnostic work-

up of microbiological samples were not performed according to a standardized protocol in the same way in all patients. For the same reason there was no standardized assessment of a patient's cardiopulmonary status prior bronchoscopy. Secondly, there were some differences in patient characteristics, e.g., patients in the NHM group were younger and had a higher prevalence of chronic lung diseases. Finally, we had to rely on patient records to determine the occurrence of AEs and SAEs. All these factors could lead to bias when comparing complication rates between the groups. These limitations could only be overcome by a randomized clinical trial comparing clinical management and outcome in patients undergoing or not undergoing flexible bronchoscopy for the diagnosis of pulmonary infections, though the conception of such a study would be very difficult.

Despite these shortcomings, this study, performed in a large patient cohort for the first time showed that diagnostic yield and the occurrence of complications were comparable when performing flexible bronchoscopy for the investigation of pulmonary infection both in patients with and without underlying hematological malignancy.

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Footnote

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-835

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-835). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Data analysis was done with regard to the Declaration of Helsinki (as revised in 2013). The Institutional Ethical Review Board for Human Studies at RWTH ("Rheinisch-Westfälische Technische Hochschule") University was involved and confirmed that a formal approval was not required as this retrospective analysis required neither an intervention nor irregularity of privacy or anonymity (EK 099/17). Individual patient consent was waived by the Review Board due to the observational nature of the study.

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