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Dagmar Kuehnhardt, Manja Hannemann, Bernd Schmidt, Ulrike Heider, Kurt Possinger, Jan Eucker

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Therapeutic implication of BAL in patients with neutropenia

Dagmar Kuehnhardt · Manja Hannemann ·
Bernd Schmidt · Ulrike Heider · Kurt Possinger ·
Jan Eucker

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Abstract Bronchoalveolar lavage (BAL) is a practicable procedure establishing the etiology of pneumonia. In patients with neutropenia, empirical antimicrobial treatment is mandatory immediately after diagnosis of infection, usually before results of BAL are available. We evaluated the impact of BAL on treatment and outcome of pneumonia in immunocompromised patients with a special regard to neutropenia. Bronchoscopy with BAL was performed in 58 episodes of clinical documented pneumonia in patients with hematological malignancies (88%) or solid tumors (12%), in 30 cases patients had neutropenia, in 28 cases patients had no neutropenia. In 93% of cases, BAL was performed under empirical antimicrobial treatment. BAL fluid was cultivated for bacteria, fungi, and tested for *Pneumocystis jirovecii* and cytomegalovirus (CMV). BAL revealed positive bacterial results in 67% of cases. Gram-positive microorganisms were detected in 95% of positive BAL results, gram-negative microorganisms in 23%, mixed bacterial cultures occurred in 41%. Positive fungi cultures were found in 59%. *P. jirovecii* was detected in 5% of cases tested and CMV in 8%. There was no significant difference between neutropenic and non-neutropenic patients. BAL results directed a change of therapy in only six of 58 episodes (5%). Overall mortality related to pneumonia was 16%. In this patient setting, the yield of BAL rarely has a

significant influence on treatment and outcome of pneumonia. The early beginning of antimicrobial treatment reduces the diagnostic yield of BAL. In patients with pneumonia during neutropenia, its use should be well considered.

Keywords BAL · Pneumonia · Neutropenia

Introduction

Immunocompromised patients constitute a heterogenous group and include patients with hematological malignancies and solid tumors, patients undergoing chemotherapy, patients after autologous and allogeneic bone marrow transplantation or patients after solid organ transplantation, as well as patients with primary immunodeficiency or acquired immunodeficiency. In patients with malignant disease, one of the most important known risk factors for infections is neutropenia. Several studies have proven the risk and analyzed the duration of neutropenia as a special risk factor [1, 6, 10]. Infections during neutropenia are a major cause of complications and mortality in patients treated with chemotherapy [23]. Among these infections, pneumonia is a very serious complication and has a poor prognosis, especially if treatment is delayed [10, 11, 31]. Patients with neutropenia should be treated immediately after onset of fever or any sign of infection and antimicrobial treatment should be initiated according to published guidelines even if positive diagnostic results are still lacking [13, 16, 18, 19].

Bronchoalveolar lavage (BAL) is a helpful procedure to establish diagnosis and clarify the etiology of pneumonia. It has been shown in patients with different kinds of immunosuppression that BAL may provide a diagnostic yield in 13 to 60% of cases [2, 8, 14, 15, 24, 25, 29]; but

D. Kuehnhardt · M. Hannemann · U. Heider · K. Possinger ·
J. Eucker (✉)
Department of Oncology and Hematology,
University Hospital Charité,
10117 Berlin, Germany
e-mail: jan.eucker@charite.de

B. Schmidt
Department of Pulmonology, University Hospital Charité,
Berlin, Germany

there exists only a few data concerning BAL in patients with pneumonia during neutropenia [3, 5, 9, 11, 21, 27, 30]. Maschmeyer et al. [19] recommended BAL in febrile neutropenic patients not responding to empirical antimicrobial therapy, in case of positive chest radiography findings. Bronchoscopy with BAL is considered as a safe procedure [21], but especially in severely ill patients, this intervention is associated with a high complication rate [2]. The long-term benefit of this procedure is difficult to demonstrate.

It is a question if BAL should be used frequently in immunocompromised patients with pneumonia or if its use should be restricted to special questions like the detection of *Pneumocystis jirovecii* pneumonia, cytomegalovirus (CMV) pneumonia, or tuberculosis.

To determine the diagnostic yield and therapeutic implication of BAL in patients with hematological diseases and solid tumors, we reviewed the experience of our Cancer Center with a special focus to neutropenia.

Materials and methods

Characteristics

We studied retrospectively the patients who underwent bronchoscopy and BAL during six consecutive years (1999–2004) in the Department of Hematology and Oncology of the university hospital Charité, Berlin. The study comprised 58 episodes of documented pneumonia in patients with hematological malignancies and solid tumors who underwent BAL. The study evaluated retrospectively the influence of diagnostic bronchoscopy with BAL on treatment and outcome of pneumonia in patients with and without neutropenia. Biopsies were not included in the analysis. We reviewed 86 charts; in 27 cases, bronchoscopy was performed due to non-infectious reasons and was excluded. One episode of pneumonia was not evaluated and excluded because of a relevant lack of clinical, microbiological, or radiographic reports.

From these 58 evaluable cases, 30 episodes occurred during neutropenia (group A) and 28 episodes occurred in non-neutropenic patients (group B). A patient was evaluated as neutropenic if at time of diagnosis of pneumonia, neutropenia <1,000/μl was present. Patient characteristics are shown in Table 1.

The diagnosis of pneumonia was based on clinical symptoms and laboratory signs of infection (fever >38°C, purulent sputum, C-reactive protein), new or progressive infiltrates on the chest radiograph and on high-resolution computed tomography (CT). Empirical antimicrobial treatment was begun promptly after onset of infection signs according to published guidelines [13, 16]. Prior to BAL, in case of any sign of infection including fever of unknown

origin, samples were taken from suspected infectious site before antimicrobial treatment was started. A thorough physical examination was performed and a chest radiograph was taken. If chest radiograph revealed pulmonary changes which were not highly suspicious on pneumonia, high-resolution CT was performed to help distinguish pneumonia from other pulmonary diseases. Pneumonia was unlikely if CT scan revealed a negative result as high-resolution CT has a high negative predictive value [12].

BAL and microbiological methods

BAL was performed under mild sedation (midazolam) and local anesthesia (lidocaine) after overnight fasting. We used fiber-optic bronchoscopes with a 2.0–2.2-mm working channel (Olympus, Pentax) via the transoral approach. Bronchoalveolar lavage was performed by wedging the tip of the bronchoscope into the segmental or sub-segmental bronchus in the area with the greatest radiologic abnormality. When bilateral changes were present, BAL was performed in the middle lobe. Sterile saline (150 mL; 0.9%) warmed to body temperature was instilled in 20-mL aliquots. Gentle manual suction with a syringe was applied to retrieve the saline. In case of respiratory failure, the amount of fluid was reduced to 80 mL. Bronchoalveolar lavage fluid was collected and immediately carried to the laboratory. Contraindications for bronchoscopy and BAL were bleeding abnormalities, acute asthma, or respiratory insufficiency (hypercapnia >44 mmHg, hypoxia <60 mmHg), severe cardiac disease or if clinical assessment indicated that oxygen and hemodynamic status might be compromised by the procedure.

Cases of pneumonia were evaluable if BAL fluid was at least processed for microscopic examination, bacterial and fungal culture. Samples were analyzed microscopically after staining with Gram stain and calcofluor white fluorescence stain for the detection of microorganisms. We did not focus on the evaluation of the cytologic pattern of BAL since it was shown in other investigations that the therapeutic usefulness of cytological examination was very low in hematological patients with chemotherapy and antibiotics prior to BAL [5, 9]. Quantitative bacterial and fungal cultures were performed according to generally accepted methods. Colony counts were determined, and identification obtained for each microorganism. In case of positive cultures, resistance to antimicrobial agents was tested. In 42 of 58 cases, BAL fluid was examined for *P. jirovecii*, and in 39 of 58 cases for CMV additionally. *P. jirovecii* antigen was diagnosed by a direct fluorescence antibody. For detection of CMV antigen and CMV DNA, direct immunofluorescence and polymerase chain reaction were performed, respectively. *Aspergillus* antigen and PCR have not been performed routinely.

Table 1 Main clinical characteristics. Group A (neutrophile count <1,000/ μ l), group B (neutrophile count >1,000/ μ l)

	Group A	Group B	Overall
Number of pneumonia	30	28	58
Median age [years] of patients, (range)	42 (16–67)	44 (17–77)	43 (16–77)
Number of female/ male	8/22	13/15	21/37
Number of patients with			
Acute leukemia/ MDS	12	3	15
Chronic myeloid leukemia	1	6	7
Lymphoma, incl. CLL	16	13	29
Solid tumor	1	6	7
Number of previous chemotherapies			
1	21	10	31
2-3	6	15	21
>3	3	2	5
Autologous transplantation	3	3	6
Allogeneic transplantation	0	2	2
Median duration of neutropenia [days], (range)			
Neutropenia <1000/ μ l	10 (3–46)		
Neutropenia <500/ μ l	8.5 (1–37)		
Number of patients with G-CSF	22	4	26
Number of patients with			
Antibacterial prophylaxis	15	5	20
Antifungal prophylaxis	4	1	5
Antiviral prophylaxis	1	0	1
Median duration of prophylaxis [days], range	11	22	12.5 (3–190)
Number of patients with antimicrobial first-line treatment started before BAL	28	26	54
Median number of treatment regimes prior to BAL (range)	2	1	1.5 (0–5)
Median duration of prior treatment [days], (range)	6.5	6	6.5 (1–28)

All data refer to the number of episodes of pneumonia

BAL fluid culture for bacteria is usually considered as clinically relevant if $\geq 10^4$ cfu/ml was detected. As BAL was performed under antimicrobial treatment in this study, and as it is known that antimicrobial treatment prior to BAL reduces the sensitivity of BAL cultures, we decided to consider bacterial cultures to be positive even if $< 10^4$ cfu/ml was detected.

The impact of bronchoscopy and BAL on treatment was evaluated from review of all progress notes and physician orders following the procedure. Treatment changes were recorded if they were made based on either a positive or negative result obtained from BAL. Therapeutic changes included addition and change of antimicrobial therapy when a pathogen was identified or discontinuation of empirical therapy when specific organisms were not found.

Statistical analyses

Data were analyzed by descriptive statistical methods using the statistical program SPSS. The Mann–Whitney *U* test

was used for unpaired, non-parametrical data, and chi-square test for comparison of qualitative variables. *P* values <0.05 were considered significant.

Results

Fifty-eight episodes of pneumonia that underwent bronchoscopy and BAL due to clinically documented or suspected pneumonia were evaluable. Patients' median age was 43 years (range 16–77). Of 43 patients, one patient underwent four bronchoscopies, one patient three bronchoscopies, and ten patients had two bronchoscopies. In four patients, BAL was performed two times during the same episode of pneumonia, but with at least 6 days time interval. We considered these episodes as independent. In 88% of cases, patients had hematological diseases and in 12% of cases, patients had solid tumors (Table 1). Six patients underwent autologous hematopoietic stem cell transplantation and two had allogeneic stem cell transplan-

tation in history. The most common underlying disease was non-Hodgkin lymphoma (Table 1). None of the patients had artificial ventilation before BAL. Of 30 patients with neutropenia, 26 (87%) had at least neutropenia $<500/\mu\text{l}$. Very severe neutropenia ($<100/\mu\text{l}$) occurred in 18 (60%) of patients. Median duration of neutropenia was 10 days (range 3–46 days). Overall, 45% of patients received granulocyte colony stimulating factor (G-CSF), 73% in group A and 14% in group B.

In 93% of cases, BAL was performed under antimicrobial treatment, 93% in group A as well as in group B. In 40% of cases, patients had received antimicrobial prophylaxis before the beginning of infection, 57% in group A and 21% in group B. Thirty-five percent of patients received antibacterial prophylaxis (cotrimoxazole, colistin, levofloxacin, ofloxacin), 9% antifungal prophylaxis (fluconazole, itraconazole), and 2% antiviral prophylaxis (aciclovir). The median duration of antimicrobial prophylaxis was 12.5 days (range 3–190 days). Fifty-one patients (88%) received antimicrobial first-line treatment according to international guidelines [13, 16], 97% of patients in group A and 79% in group B. These empirical regimen included ciprofloxacin plus amoxicillin–clavulanate, monotherapy with fourth-generation cephalosporin or carbapenem, antipseudomonal penicillin plus aminoglycoside and/or vancomycin, fourth-generation cephalosporin plus aminoglycoside and/or vancomycin, carbapenem plus aminoglycoside and/or vancomycin. Forty-one percent of patients received antifungal treatment as a part of the first-line treatment of pneumonia (amphotericin B, imidazole). In 50% of patients, antimicrobial treatment regimes were changed prior to BAL, up to five treatment regimes with a median of 1.5 treatment regimes were applied prior to BAL. Overall, the median duration of prior antimicrobial treatment (including first-line and following treatments due to any infection) was 6.5 days (range 1–28 days) with a median of 6.5 days in the group with neutropenia and 6 days in the group without neutropenia.

Clinical results

All patients had clinically documented pneumonia at time of BAL. According to the criteria of the American College of Chest Physicians and Society of Critical Care Medicine [20], in 71% of investigated periods, patients showed signs of sepsis, in 19%, severe sepsis was diagnosed and 9% developed septic shock during the treatment period. Chest radiograph showed signs of infection in most cases, 93% in group A and 97% in group B. Overall, high-resolution CT was performed prior to BAL in 39 of 58 (67%) cases to further characterize pulmonary alteration seen in chest radiograph or in cases of suspected pneumonia with negative results in chest radiograph. Radiological diagnosis

of atypical pneumonia was made in 46 of 58 cases (79%). *P. jirovecii* pneumonia and CMV pneumonia was suspected due radiological signs each in two cases.

Microbiological results

BAL revealed positive bacterial results in overall 67% of cases. There was no significant difference between neutropenic (57%) and non-neutropenic (79%) episodes ($p=0.076$). Gram-positive bacteria were the most common isolated microorganisms. Gram-positive microorganisms were detected in 95% of positive BAL results, gram-negative microorganisms in 23%, mixed bacterial cultures occurred in 24 cases (41%). The major pathogens detected were coagulase-negative staphylococci (80%), *Streptococcus* species (51%), *Enterococcus* species (18%), *Prevotella* species (15%), *Pseudomonas aeruginosa* (5%), and *Staphylococcus aureus* (5%; Table 2).

Only 17 of 39 (44%) cases with positive BAL culture for bacteria showed at least 10^4 cfu/ml. If the cut-off was set at $\geq 10^4$ cfu/ml, only in 17 of 58 (29%) cases has a positive culture result been obtained, in group A 20% and in group B 39% of cases ($p=0.2$). Among these, all positive cultures contained gram-positive bacteria; in 41% gram-negative bacteria were detected additionally. Accordingly, the main agents were coagulase-negative staphylococci (77%), *Streptococcus* species (47%), *Enterococcus* species (29%), *Prevotella* species (24%), and *P. aeruginosa* (12%; Table 3).

Fungi were detected in 59% of cases. There was no significant difference between neutropenic and non-neutropenic patients ($p=0.9$). All fungi detected were *Candida* species. Most frequent fungi were *Candida albicans* and *Candida glabrata* (each 50%; Table 2). In four of 32 positive fungal cultures, more than one *Candida* species was detected.

In 39 cases, a CMV infection was suspected. Of these, 62% had a positive reaction of CMV antigen but in only 8% CMV PCR revealed a positive result, one case in group A and two cases in group B ($p=0.4$). *P. jirovecii* antigen was detected in two of 42 cases tested, both cases appeared in the non-neutropenic group ($p=0.1$; Table 4).

Blood cultures revealed positive results in 10 of 58 cases (17%), 27% in neutropenic patients, 7% in non-neutropenic patients. Seventy percent of bacteremia was due to gram-positive bacteria and 30% due to gram-negative bacteria. No fungemia was detected. Only in one case of all patients with positive BAL results did blood cultures reveal a consistent positive result; in this case, in group B *P. aeruginosa* was detected in both cultures.

Sputum cultures revealed positive results in 27 of 58 cases (47%). In most cases (93%), *Candida* species were detected; furthermore, in 17 cases, gram-positive bacteria and in five cases, gram-negative bacteria were detected.

Table 2 Diagnostic yield of BAL in 58 episodes of pneumonia

	Group A	Group B	Overall
Bacteria (total)	17/30 (57%)	22/28 (79%)	39/58 (67%)
Gram-positive bacteria	17/17 (100%)	20/22 (91%)	37/39 (95%)
Gram-negative bacteria	1/17 (6%)	8/22 (36%)	9/39 (23%)
Coagulase-negative staphylococci	16/17 (94%)	15/22 (68%)	31/39 (80%)
<i>Streptococcus</i> species	10/17 (59%)	10/22 (45%)	20/39 (51%)
<i>Enterococcus</i> species	1/17 (6%)	6/22 (27%)	7/39 (18%)
<i>Pseudomonas aeruginosa</i>	1/17 (6%)	1/22 (5%)	2/39 (5%)
<i>Stenotrophomonas maltophilia</i>	0	1/22 (5%)	1/39 (3%)
<i>Klebsiella pneumoniae</i>	0	1/22 (5%)	1/39 (3%)
<i>Staphylococcus aureus</i>	0	2/39 (5%)	2/39 (5%)
<i>Haemophilus</i> species	0	1/39 (3%)	1/39 (3%)
<i>Prevotella</i> species	0	6/22 (27%)	6/39 (15%)
<i>Veillonella</i> species	0	3/22 (14%)	3/39 (8%)
<i>Bifidobacterium adolescentis</i>	0	1/22 (5%)	1/39 (3%)
<i>Fusobacterium nucleatum</i>	0	1/22 (5%)	1/39 (3%)
Fungus (total)	17/29 (59%)	15/25 (60%)	32/54 (59%)
<i>Candida albicans</i>	8/17 (47%)	8/15 (53%)	16/32 (50%)
<i>Candida glabrata</i>	9/17 (53%)	7/15 (47%)	16/32 (50%)
<i>Candida guilliermondii</i>	1/17 (6%)	0	1/32 (3%)
<i>Candida krusei</i>	0	1/15 (7%)	1/32 (3%)
<i>Candida parapsilosis</i>	0	1/15 (7%)	1/32 (3%)
Yeast (not differentiated)	0	1/15 (7%)	1/32 (3%)
<i>Aspergillus</i> species	0	0	0

In 24 of 39 positive cultures, more than one bacteria was detected. In four of 32 positive cultures, more than one fungus was detected

Only in two cases did sputum cultures show the same results as BAL cultures; in one case, *S. aureus* and in another case, *P. aeruginosa* was detected and both cases appeared in the non-neutropenic group.

As described before, in 93% of cases, BAL was performed under antimicrobial treatment, and in 35% of cases, patients received antibacterial prophylaxis. Positive

bacterial BAL results, for gram-positive as well as for gram-negative bacteria, were significantly less common in patients who underwent antibacterial prophylaxis than in patients who did not ($p=0.042$). Neither the duration of empirical antimicrobial treatment nor the number of antimicrobial treatment regimes prior to BAL (started after onset of signs of infection) had a significant influence on a

Table 3 Diagnostic yield of BAL in 58 episodes of pneumonia

	Group A	Group B	Overall
Bacteria (total)	6/30 (20%)	11/28 (39%)	17/58 (29%)
Gram-positive bacteria	6/6 (100%)	11/11 (100%)	17/17 (100%)
Gram-negative bacteria	1/6 (17%)	6/11 (55%)	7/17 (41%)
Coagulase-negative staphylococci	6/6 (100%)	7/11 (64%)	13/17 (77%)
<i>Streptococcus</i> species	2/6 (33%)	6/11 (55%)	8/17 (47%)
<i>Enterococcus</i> species	1/6 (17%)	4/11 (36%)	5/17 (29%)
<i>Pseudomonas aeruginosa</i>	1/6 (17%)	1/11 (9%)	2/17 (12%)
<i>Klebsiella pneumoniae</i>	0	1/11 (9%)	1/17 (6%)
<i>Staphylococcus aureus</i>	0	1/11 (9%)	1/17 (6%)
<i>Haemophilus</i> species	0	1/11 (9%)	1/17 (6%)
<i>Prevotella</i> species	0	4/11 (36%)	4/17 (24%)
<i>Veillonella</i> species	0	2/11 (18%)	2/17 (12%)
<i>Bifidobacterium adolescentis</i>	0	1/11 (9%)	1/17 (6%)
<i>Fusobacterium nucleatum</i>	0	1/11 (9%)	1/17 (6%)

Only bacterial cultures with more than 10^4 cfu/ml were regarded as relevant

Table 4 Virological results and detection of *Pneumocystis jirovecii*: diagnostic yield of BAL in 58 episodes of pneumonia

	Group A	Group B	Overall
CMV antigen	9/19 (47%)	15/20 (75%)	24/39 (62%)
CMV DNA	1/21 (5%)	2/17 (12%)	3/38 (8%)
<i>Pneumocystis jirovecii</i>	0/24	2/18 (11%)	2/42 (5%)

positive or negative bacterial result of the BAL ($p=0.2$ and $p=0.6$, respectively).

Therapeutic impact of BAL

Overall, BAL results directed a change of therapy in six of all cases (11%), two in group A (7%) and four in group B (14%). In one case in group A, the detection of CMV antigen in BAL led to the addition of ganciclovir to the antimicrobial treatment, in another case, a treatment with amphotericin B was begun due to the detection of *C. albicans* in the BAL. In one non-neutropenic patient, the detection of alpha-hemolytic streptococci in bacterial culture led to a change of therapy, a treatment with penicillin G was started. In two non-neutropenic patients, the detection of *C. albicans* resulted in a change of therapy and in one patient, the detection of *P. jirovecii* in BAL fluid led to the addition of cotrimoxazole to the antimicrobial treatment. Focusing on bacteria, only in one of 58 cases did a positive bacterial culture cause a change of antimicrobial treatment. This patient belonged to group B.

Concerning *P. jirovecii* and CMV, in group A, only one patient was diagnosed with CMV pneumonia and in group B, two patients were diagnosed with *P. jirovecii* pneumonia and another two patients with CMV pneumonia. So, in most patients with radiological signs of atypical pneumonia (89%), *P. jirovecii* pneumonia and CMV pneumonia whose antimicrobial therapy is associated with intensive side effects especially for the hematopoietic system could be excluded via BAL.

Complications due to bronchoscopy and BAL occurred in four of 58 cases (7%), 7% in group A as well as in group B. Complications included hypotension, hypoxia, and pneumothorax. Overall, 11 patients (19%) died during the study period, six in group A, five in group B. Of these patients, nine died due to infection. Overall mortality related to pneumonia was 16%. There was no significant difference in mortality between neutropenic and non-neutropenic patients ($p=0.8$). There was either no difference in mortality rate for cases with positive or negative BAL results ($p=0.3$). In the group of patients that BAL results guided further antimicrobial therapy, one patient died due to an *Aspergillus* pneumonia that was detected post mortem.

Discussion

BAL is a helpful diagnostic tool to establish diagnosis and clarify the etiology of pneumonia. There exist some data that support a frequent use of BAL in immunocompromised patients with pulmonary infiltrates [8, 14, 21]. But, especially in severely ill patients with neutropenia, BAL is associated with a high rate of complications [2, 11, 30]. Therefore, the application of BAL in this setting should be considered carefully. This study highlights, in a critical way, the importance of BAL in patients with lung infiltrates and neutropenia.

The diagnostic yield of BAL published for neutropenic patients with pneumonia ranged between 13% and 53% [3, 5, 9, 11, 21, 27, 30]. Nearly all of these data were collected in retrospective studies.

In neutropenic patients with infection, prompt antimicrobial treatment is mandatory and it should not be delayed by any diagnostic procedure [7, 13, 23]. Additionally, most neutropenic patients with pneumonia receive antifungal drugs according to international guidelines [16, 18, 19, 26]. It is known that previous antimicrobial treatment lowers the yield of BAL culture and is probably responsible for the low impact on treatment changes [4, 5, 7, 9, 30]. We could demonstrate as well, that positive bacterial BAL results were significantly less common in patients who underwent antibacterial prophylaxis than in patients who did not.

Concerning the patient collective, our results were comparable to the data of Cordonnier et al. [5] as we used similar definitions of the neutropenic and non-neutropenic subgroup. The diagnostic yield of BAL (53%) was comparable to our study and did not differ significantly between the two subgroups. However, in their study, BAL results led to changes in therapy in more than one third of cases. In contrast, we observed a change of treatment in only 11% of cases. Saito et al. [27] emphasized the poor therapeutic usefulness of BAL in neutropenic patients with hematological diseases. Their BAL results were compared in seven patients with those at autopsy performed within 3 weeks of BAL. Overall, the diagnostic yield was low (15%), only one etiologic diagnosis by BAL and autopsy corresponded. Azoulay et al. [2] even demonstrated that in critically ill hematological and oncological patients with acute respiratory failure, non-invasive strategies had a higher diagnostic yield than bronchoscopy and BAL. On the other hand, the studies of Dunagan et al. [8], Hummel et al. [14], and Peikert et al. [21] were in favor for the application of BAL in immunocompromised patients. They stated good diagnostic yield and frequent therapeutic implications in more than 50% of patients, although an impact on survival could not be demonstrated.

It is remarkable that in our study the results of neutropenic and non-neutropenic patients are comparable.

The relatively slight difference between the two groups concerning BAL results and therapeutic implications of BAL may be due to the fact that even group B patients were considered as immunocompromised, according to the definition of Jain et al. [15]. For, even if they were not neutropenic at the time of BAL, most of them had undergone chemotherapy and experienced some episodes of neutropenia as well.

As BAL was performed in 93% of cases under antimicrobial treatment in both groups, we decided to consider bacterial cultures to be positive even if $<10^4$ cfu/ml were detected [22]. In spite of this low cut-off in pretreated patients, the therapeutic consequences of bacterial BAL results remained rare, only one of the antimicrobial treatment changes in our study was due to results of bacterial cultures. This further supports the low impact of BAL on treatment. Similar in fungal pathogens, there was a high rate of positive cultures for *Candida* species. However, the probability of a *Candida* pneumonia is very low. Since *Candida* species belong to the physiological flora of the gastrointestinal tract, evidence of *Candida* in BAL has to be regarded as contamination until invasive disease is proven by lung biopsy [19, 26]. In our study *Candida* pneumonia could not be proven in any case. Nevertheless, in three cases, a change of treatment was performed due to detection of *Candida* species that retrospectively had to be considered as clinically irrelevant. Knowing the disadvantages of a retrospective study, we abstained from evaluating the accuracy and probability of etiologic diagnosis, which had been made with the aid of BAL results. We did not evaluate if results were false positive or negative, but we evaluated the impact on antimicrobial treatment and we stated that the high amount of bacterial results, independent of the chosen cut-off, did not result in any treatment change. However, this cognition does not affect the importance of BAL in detecting or excluding *P. jirovecii* pneumonia or CMV pneumonia.

The bacterial spectrum isolated in our patients corresponded to the spectrum obtained in other studies in immunocompromised host with *Streptococcus* and *Staphylococcus* species isolated most frequently [7, 9, 11]. Most common organisms found in immunocompromised patients by Eriksson et al. [9] were alpha-hemolytic streptococci, coagulase-negative staphylococci, enterococci, and *Neisseria* species. *P. aeruginosa* was the most frequent gram-negative microorganism detected corresponding with other data in hematological malignancies [11]. But the significance of alpha-hemolytic streptococci, enterococci, and coagulase-negative staphylococci obtained from BAL culture remains unclear, since most of them occur as commensals and rarely cause pneumonia. Maschmeyer et al. [19] defined the isolation of these microorganisms from BAL fluid as etiologically insignificant findings for lung

infiltrates. However, there are some authors suggesting that immunocompromised patients may develop pneumonia from these microorganisms [7, 17, 28].

In our study, overall mortality related to pneumonia was 16%. There was no difference in mortality rate for cases with positive or negative BAL results. As detection of microorganism in BAL did not lead to a relevant rate of antimicrobial treatment changes, BAL results had probably no influence on mortality. The rate of BAL-associated complications was very low in our study (7%). This might be related to the retrospective character of the study and eventually missing documentation of minor complications.

Conclusion

BAL had a low impact on antimicrobial treatment. We summarize that the significance of BAL has decreased and its use should be considered with care in patients with pneumonia during neutropenia. However, this thesis based on a retrospective analysis should be tested in a prospective study. Nevertheless, we are convinced that BAL is still of high diagnostic value to distinguish between pulmonary tumor infiltration and pneumonic infiltration or to detect specific infections like *P. jirovecii* or CMV pneumonia.

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