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BRIEF COMMUNICATION

Broncho-alveolar lavage in patients with acute respiratory distress syndrome due to COVID-19

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Abstract

As data about microbiological testing and the cellular composition of the broncho-alveolar lavage (BAL) fluid in patients ventilated due to coronavirus disease 2019 (COVID-19) are lacking, this was investigated in a retrospective analysis ($n = 58$). Co-infection with pathogens was detected in 31 patients, whereas the analysis of BAL cellularity showed an increased total cell count and an alveolitis dominated by neutrophils. None of the physicians performing bronchoscopies in COVID-19 patients had serological evidence of severe acute respiratory syndrome coronavirus 2 infection.

Although most individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) suffer from mild symptoms only, the disease can progress to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation.[1–3] Currently, there is no consensus whether flexible bronchoscopy with broncho-alveolar lavage (BAL) should be performed in these patients due to the risk for aerosol-transmitted infection for healthcare workers.[4] However, the procedure can provide important information, as BAL can reveal the presence of microbiological agents apart from SARS-CoV-2 requiring antibiotic of antifungal treatment. Furthermore, there is limited evidence about the cellular composition of BAL fluid during severe coronavirus disease 2019 (COVID-19)-associated pneumonia.

BAL fluid cellularity has been used in numerous animal studies of ARDS to monitor inflammation in the alveolar space and an association of increased BAL fluid neutrophils and a poor survival rate in human ARDS has been demonstrated, although this parameter is not part of the clinical routine.[5,6] Bronchoscopy including BAL is routinely performed in our institution for the diagnostic work-up of ARDS, which remained unchanged during the COVID-19 pandemic. Hence, results from microbiological testing and the cellular composition of the BAL fluid in patients ventilated for severe COVID-19 were analysed.

Data from all patients admitted to our institution with ARDS due to COVID-19 between 24 February and 3 November who had received flexible bronchoscopy including BAL were evaluated retrospectively. The diagnosis of COVID-19 was made on the basis of a positive SARS-CoV-2 result in respiratory material.[7] Data analysis was done with regard to the Declaration of Helsinki. According to the local Institutional Review Board for Human Studies, a formal approval was not required for this analysis due to the retrospective nature of the study and notification to the Institutional Review Board for Human Studies was considered adequate (EK 080/20). BAL was performed using flexible bronchoscopes (Olympus, Tokyo, Japan). The bronchoscope was wedged into a segment where lung infiltration was present or was most severe. A total of 160 mL sterile saline solution was instilled into aliquots of 20 mL and the fluid was recovered by aspiration. Samples were sent for microbiological and virological testing, as well as for cytological analysis. Standard personal protection equipment including FFP-2 masks was worn by the

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performing physicians. Original data were retrieved from electronic patient record systems (Medico, Siemens, Erlangen, Germany and ICCA, Philips Health Systems, Hamburg, Germany) and collected in a database. Demographic data (age and sex), data about treatment in the intensive care unit (days on ventilator) and findings from BAL (culture results and cytology) were recorded. Antibody testing for SARS-CoV-2 was performed on all physicians ($n = 5$) who had done the bronchoscopies using a commercially available enzyme-linked immunosorbent assay (Euroimmun, Lübeck, Germany). Statistical analysis was performed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA). Unless otherwise stated, all data are presented as mean ± standard deviation (normally distributed data) or median (interquartile range (IQR)) (non-normally distributed data). Two-group comparisons were performed using the Wilcoxon signed-rank test. Statistical significance was defined as a P-value of <0.05.

Table 1 Patient data and results from BAL fluid analysis

	Patients ($n = 58$)
Patient demographic data	
Age (years)	60.5 (54.75; 68)
Male (*n*)	43 (74.1)
Time point of BAL	
Interval from initiation of invasive ventilation to BAL	3 (1; 7.5)
Interval from onset of symptoms to BAL	14 (9; 17.75)†
Microbiological yield (%)	
Overall diagnostic yield	53.4
Diagnostic yield for bacteria	37.9
Diagnostic yield for fungi	13.8
Diagnostic yield for viruses (apart from SARS-COVID-19)	10.3
BAL cell counts	
Total cell count ($\times 10^6$ cells)	22.4 (10.72; 44.36)
Monocytes/macrophages (%)	7.84 (5.29; 15.6)
Monocytes/macrophages ($\times 10^6$ cells)	58 (29.25; 74)
Neutrophils (%)	35.5 (22.5; 61.25)
Neutrophils ($\times 10^6$ cells)	5.99 (2.34; 18.41)
Lymphocytes (%)	2 (0; 3)
Lymphocytes ($\times 10^6$ cells)	1.32 (0; 1.97)

Data are presented as median (interquartile range) or number of patients (%).

†Data were available for 52 patients.

BAL, broncho-alveolar lavage; COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome.

BAL was performed for 58 patients treated at our institution for COVID-19-associated ARDS. Patient characteristics and details concerning microbiological yield of the BAL fluid are summarised in Table 1. The overall microbiological yield (any bacteria, fungi or viruses apart from SARS-CoV-2) was 53.4%. Bacteria were detected most frequently (diagnostic yield: 37.9%), whereas the detection rate of fungi (13.8%) and viruses (10.3%) apart from SARS-CoV-2 was low. Testing of the BAL fluid for SARS-CoV-2 was done in 56 out of 58 patients of whom 42 (75%) were tested positive. Univariate analysis revealed an association between the probability of a negative SARS-CoV-2 polymerase chain reaction (PCR) test and the duration from the onset of symptoms until BAL was done ($P = 0.0115$). Among the different cell types, monocytes/macrophages were most abundant in BAL fluid followed by neutrophils and lymphocytes (Table 1, Fig. 1). Total cell count (36.2×10^6 (IQR 16.6–53.4) vs 15.8×10^6 (IQR 10.1–37.5); $P = 0.0232$) and the number of neutrophils (14.3×10^6 (IQR 4.3–25.5) vs 5.2×10^6 (IQR 1.9–11.9); $P = 0.0376$) were significantly increased in BAL samples positive for bacteria. We did not find an association of BAL cellularity with clinical parameters, for example, survival, ventilator days, need for extracorporeal membrane oxygenation or time span from the onset of symptoms/initiation of invasive

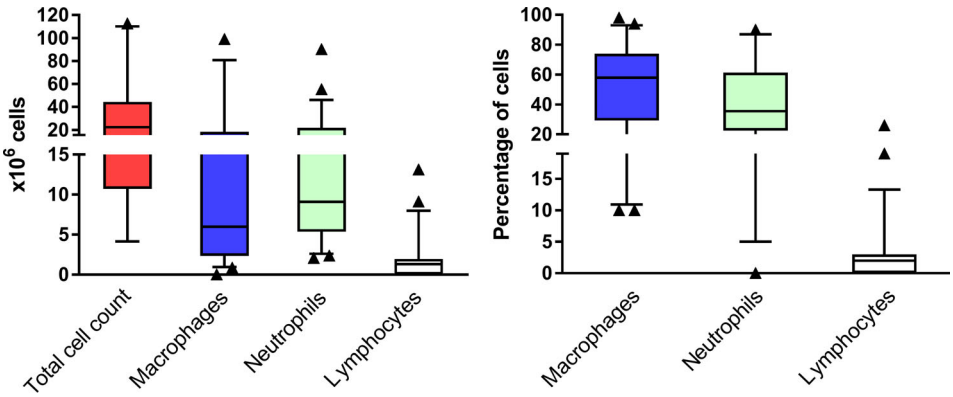

Figure 1 Total and differential cell count in broncho-alveolar lavage (BAL) fluid. Total cell counts, as well as the number of macrophages, neutrophils and lymphocytes (left). Percentage of different cells in BAL fluid (right). Boxes represent the interquartile range and whiskers the 5–95% percentile.

ventilation to BAL. All bronchoscopies with BAL were done by a total of five physicians, which were tested negative for SARS-CoV-2 infection by serology in all cases.

Discussion

In the present study, we describe microbiological results and the cellular composition of BAL in patients with COVID-19 requiring mechanical ventilation. A considerable proportion of patients (53.4%) was tested positive for other microbiological agents, mainly bacteria, apart from SARS-CoV-2. Recently, a study demonstrated that the prevalence of co-infection with additional pathogens was even higher (more than 90%) among patients infected with SARS-CoV-2 and was highest among patients with severe COVID-19. However, as this study used a PCR-based technique for the detection of pathogens in throat swabs, it is difficult to determine whether this reflects clinically relevant pulmonary infection rather than infection of the upper respiratory tract or colonisation.[8] In addition, a considerable proportion of patients was tested negative for SARS-CoV-2 in the BAL fluid, likely due to the variability in the time span from the onset of symptoms until BAL was performed.

So far, no study has investigated the cellular composition of BAL in patients with COVID-19-associated ARDS. According to other forms of ARDS, we found an increased total cell count and an increased number of neutrophils. As expected, the number of cells was higher in patients suffering from bacterial co-infection. Nevertheless, total cell count or cellular composition was not associated with any clinical end points possibly due to the small sample size and the variability of the time points until BAL was performed.[5,6]

In conclusion, in patients with COVID-19 requiring mechanical ventilation, bronchoscopy with BAL seems to be safe for the endoscopist and can reveal co-infection with other pathogens thus providing important information for the guidance of antimicrobial therapy.

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