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Bronchoalveolar Lavage in Patients with COVID-19 with Invasive Mechanical Ventilation for Acute Respiratory Distress Syndrome

To the Editor:

Bronchoalveolar lavage (BAL) is a routine bronchoscopic procedure that may provide significant information for the management of pneumonia. In critically ill patients, including those with severe acute respiratory distress syndrome (ARDS), bronchoscopy and BAL safety have been demonstrated (1, 2). However, early after the coronavirus disease (COVID-19) pandemic spread, guidelines converged in recommending limiting the use of bronchoscopy and considered known or suspected COVID-19 to be a relative contraindication to bronchoscopy, as the risk of contamination to healthcare workers may be increased by this aerosol-generating procedure (3, 4). During the first wave of the pandemic, we rapidly observed, as highlighted by others (5, 6), an increased need for bronchoscopy in patients with COVID-19–associated ARDS requiring mechanical ventilation, mainly for bronchoaspiration but also, in some cases, to perform BAL for microbiological sampling. The ability of BAL to confirm COVID-19 was also demonstrated, in case of previous negative nasopharyngeal swab(s) in patients, intubated or not, with clinical concern for this diagnosis (6–8). Nevertheless, the value of BAL has not been evaluated so far for further microbiological workup after noninvasive diagnostic tests were exhausted.

For this purpose, and because data on BAL performed on patients with COVID-19–associated ARDS remain scarce, we herein describe our single-center experience at the Henri Mondor University Hospital on 28 consecutive BALs performed between March 31 and June 3, 2020, on 24 patients with COVID-19 (4 patients had two BALs) treated with invasive mechanical ventilation for moderate to severe ARDS. The median time from intubation to BAL was 16 (interquartile range [IQR], 10–21) days, and the median ratio of arterial oxygen pressure to fraction of inspired oxygen (Pa_{O_2}/FI_{O_2}), FI_{O_2}, and positive end-expiratory pressure (H_2O cm) before BAL were, respectively, 122 (IQR, 74–148), 0.8 (IQR, 0.4–1), and 8 (IQR, 5–10).

BALs were performed for a microbiological purpose in all cases: to confirm severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ($n = 2$; 7%), after one and three negative reverse transcriptase–polymerase chain reactions on nasopharyngeal swab, for a suspicion of ventilator-associated pneumonia ($n = 11$; 39%) or a suspicion of invasive aspergillosis ($n = 4$, 14%) and/or to rule out a superinfection before starting a corticosteroid course ($n = 12$; 43%). Results of routine noninvasive microbiological tests (blood cultures, protected distal aspiration for bacterial culture, tracheal aspiration for fungal culture and *Aspergillus* and *Pneumocystis* polymerase chain reaction (PCR), serum galactomannan and β-D-glucan detection, and nasopharyngeal swab for SARS-CoV-2 genome detection) were always considered before deciding whether to perform BAL.

Cytological analysis was available in most of the cases ($n = 26$, 93%). BAL fluid was frequently rich in mucus ($n = 23$, 82%), with a mean (range) BAL cellularity of 702 cells/μl (30–4,554), higher than what we usually observe in patients with ARDS without COVID-19 (personal data). Subcellular differential count is presented in Table 1. As usually observed in patients with ARDS without COVID-19 (9), BAL fluid was predominantly neutrophilic in 24 cases (92%). BAL lymphocytosis exceeded 10% in eight cases (31%), and exceeded 20% in four of these cases (15%), all respectively performed at <14 days and ≤ 10 days after intubation. Activated lymphocytes (AL) of various types, often with atypical pattern, were frequently observed ($n = 14$; 54%), especially if BAL was performed ≤ 10 days after intubation (Table 1). AL were scored either "rare-to-occasional" ($n = 6$) or "frequent-to-prominent" ($n = 8$) based on whether the lymphocyte proportion exceeded a threshold of 25%. When AL score was "frequent-to-prominent," SARS-CoV-2 reverse transcriptase–polymerase chain reaction was

Table 1. Main results of BAL (n = 28) on 24 patients with COVID-19–associated ARDS

	Time from Intubation to BAL			*P* Value*
	Overall	⩽10 d	>10 d	
Number of BALs performed	28	11	17	—
Time from symptoms onset to BAL, d	24 [18–30]	18 [16–21]	26 [24–34]	—
Time from intubation to BAL, d	14 [9–21]	7 [3–10]	20 [17–23]	—
Positive SARS-CoV-2 genome detection before BAL	25 (89)	8 (73)	17 (100)	0.14
Positive SARS-CoV-2 genome detection on latest NP swab	11 (39)	5 (45)	6 (35)	0.70
Latest PDA positive†	13 (46)	3 (27)	10 (59)	0.14
Antibacterial therapy at time of BAL	15 (54)	4 (37)	12 (71)	0.12
Antifungal therapy at time of BAL	5 (18)	1 (9)	4 (24)	0.62
BAL fluid recovery, ml	49 [38–75]	72 [45–76]	40 [35–62]	0.24
Cytological analysis of BAL				
BAL cell count, per μl	540 [305–775]	500 [310–860]	566 [266–674]	0.92
Macrophages, %	21 [14–46]	16 [10–19]	43 [15–54]	0.17
Neutrophils, %	54 [39–75]	65 [41–76]	52 [41–75]	0.98
Lymphocytes, %	6 [2–14]	17 [7–21]	4 [1–5]	**0.002**
Presence of activated lymphocytes	14 (54)	10 (91)	4 (29)	**0.004**
Eosinophils, %	1 [0–1]	0 [0–1]	1 [0–1]	0.82
Microbiological analysis of BAL				
Global microbiological yield of BAL	24 (86)	10 (91)	14 (82)	1
At least one pathogen undetected before BAL	13 (46)	6 (55)	8 (47)	1
Positive bacterial culture	14 (50)	4 (36)	10 (59)	0.44
Positive bacterial culture although latest PDA negative for this bacteria‡	8 (29)	2 (18)	6 (35)	0.41
Aspergillus (culture and/or PCR)	7 (25)	3 (27)	4 (24)	1
Positive SARS-CoV-2 genome detection on BAL	11/22 (50)	9/10 (90)	2/12 (17)	**0.002**
Positive SARS-CoV-2 genome detection on BAL although negative on latest NP swab	5/13 (38)	5/6 (83)	0/7 (0)	**0.005**
Positive SARS-CoV-2 genome detection on BAL although negative on all previous NP swabs	2/3 (67)	2/3 (67)	—	—
Other virus detected by PCR	9/21 (43)	2/10 (20)	7/11 (64)	0.08
Therapeutic impact of BAL				
Global therapeutic impact of BAL	17 (61)	8 (73)	9 (53)	0.43
Modification of antibacterial therapy§	8 (29)	4 (36)	4 (24)	0.67
Modification of antifungal therapy‖	5 (18)	1 (9)	4 (24)	0.62
Introduction of antiviral therapy	1 (4)	1 (9)	0 (0)	0.39
Decision to start corticosteroids therapy	6 (21)	3 (27)	3 (18)	0.65

Definition of abbreviations: ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; COVID-19 = coronavirus disease; NP = nasopharyngeal; PCR = polymerase chain reaction; PDA = protected distal aspiration; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
BAL volume injected was 150 ml of saline in three aliquots in all cases. Results are presented as *n* (%) or median [interquartile range].
*Bivariate statistical comparisons using Mann-Whitney *U* test or Fisher's exact test, bold typeface if $P < 0.05$.
†For bacterial culture, performed 1 [0.75–1] day before BAL, range (0–5) days.
‡Performed 1 [1–1] day before BAL, range (0–5) days.
§Introduction, switch, prolongation, or withdrawal of antibiotics; modifications of antibiotics due to last PDA results were excluded.
‖Introduction, continuation (only considered if diagnostic criteria of pulmonary aspergillosis were not obtained before BAL), or withdrawal of antifungal therapy (*see* Table 2 for details).

positive, either on BAL ($n = 7$) or on the last nasopharyngeal swab 48 hours before BAL in the case it was not performed on BAL. According to SARS-CoV-2 genome detection on BAL, AL were found in 9/11 positive cases (82%), versus 4/11 (36%) in negatives ($P = 0.08$).

BAL microbiological analysis revealed at least one pathogen in 24 cases (86%) (Table 1). When considering the results of previous less invasive microbiological tests, BAL revealed at least one previously undetected pathogen in 13 cases (46%) in culture and/or by PCR: nine bacteria, eight viruses (one cytomegalovirus, four *herpes simplex virus*-1, one rhinovirus, two SARS-CoV-2), and three *Aspergillus*. Results and final interpretation of mycological tests (9–12), including those obtained before BAL, are shown in Table 2.

Overall, BAL had an impact on medical decision-making in 20 cases (71%), with introduction ($n = 6$), continuation ($n = 3$), switch ($n = 2$), or withdrawal ($n = 4$) of antimicrobial therapy in 14 cases (50%) and/or decision to start ($n = 6$; 21%), or not ($n = 6$, 21%), corticosteroids therapy.

No immediate complication of BAL procedures occurred, but one patient experienced a significant deterioration of his condition 24 hours after BAL, requiring venovenous extracorporeal membrane oxygenation. The day after BAL, the median ratio of arterial oxygen tension/pressure to F_{IO_2} was 150 (IQR, 61 to 174), not significantly different from the baseline value ($P = 0.15$), with a median change of +22 (IQR, −54 to +33). Six patients (23%) died during follow-up, with a median time from intubation to BAL of 19 (IQR, 12 to 20) days and a median time from BAL to death of 4

Table 2. Mycological workup leading to diagnosis or exclusion of IPA in patients with SARS-CoV-2–associated ARDS undergoing BAL

Time from ICU Admission/ Intubation to BAL (*d*)	Mycology before BAL		Mycology (BAL)			Cytopathology (BAL)	Conclusions	
	Serum GM (Index)	Tracheal Aspiration*: Culture/*Aspergillus* PCR† (C_t Value)	Bronchial Aspiration: Direct Examination/Culture	BAL: Culture	BAL: *Aspergillus* PCR (C_t Value)†	Direct Examination	Final Consensus Diagnosis	Therapeutic Decision
5/0	Neg	Neg/Neg	Neg/Neg	Neg	*Aspergillus sp* (39)	Neg	Colonization	No AFT
6/6	Pos (0.8)	Neg/*Aspergillus sp* (40)	Neg/*C. albicans*	—	*A. fumigatus* (32) *Aspergillus sp* (34)	*Candida*-type hyphae	Putative IPA‡	AFT continuation
7/7	Neg	Neg/Neg	Pos/*A. fumigatus*	*A. fumigatus*	*A. fumigatus* (29) *Aspergillus sp* (29)	*Aspergillus*-type hyphae	Putative IPA‡	Start of AFT
12/12	Pos (0.7)	Neg/Neg	Pos/*A. fumigatus*	*A. fumigatus*	*A. fumigatus* (32) *Aspergillus sp* (32)	Neg	Putative IPA‡	AFT continuation
15/15	Neg	*A. fumigatus*/Neg	Neg/*A. fumigatus* & *C. albicans*	Neg	Neg	Neg	Colonization	Withdrawal of AFT
20/20	Neg	Neg/*Aspergillus sp* (38)	Neg/*A. fumigatus* & *C. albicans*	*C. albicans*	*A. fumigatus* (37) *Aspergillus sp* (37)	Neg	Probable *Aspergillus* tracheobronchitis§	AFT continuation
23/23	Pos (1.3)	*C. albicans*/Neg	Neg/*C. albicans*	*C. albicans*	Neg	Neg	False positive of serum GM	Withdrawal of AFT
26/26	Neg	*C. albicans*/Neg	Neg/*A. fumigatus* & *C. albicans*	*C. albicans*	*Aspergillus sp* (37)	Neg	Possible IPA‖	Start of AFT

Definition of abbreviations: AFT = antifungal therapy; *A. fumigatus* = *Aspergillus fumigatus*; BAL = bronchoalveolar lavage; *C. albicans* = *Candida albicans*; COVID-19 = coronavirus disease; C_t = threshold cycle; GM = galactomannan; ICU = intensive care unit; IPA = invasive pulmonary aspergillosis; Neg = negative; PCR = polymerase chain reaction; Pos = positive; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

BAL galactomannan detection was not available during the study period due to COVID-19 lab constraints.

*Last tracheal aspiration was performed at a median [interquartile range] of 2 [0–3] days before BAL, range (0–7) days.

†*Aspergillus* PCR methods: PCR specifically targeting *A. fumigatus* by 28S rRNA gene and PCR pan *Aspergillus* using mitochondrial gene.

‡Putative IPA diagnosis according to criteria initially proposed by Blot and colleagues (10) and revised by Schauwvlieghe and colleagues (11).

§Diagnosis of probable *Aspergillus* tracheobronchitis was based on the presence of airway plaque and pseudomembrane associated with microbial criteria, as recently proposed for influenza-associated pulmonary aspergillosis (12).

‖Consensus diagnosis of possible IPA was based on the presence of both positive tracheal aspiration culture and *Aspergillus* sp. PCR positivity on BAL (criteria for probable/putative *Aspergillosis* not met whatever the definition used (7–9), so colonization could not be excluded in this case).

(IQR, 2 to 11) days. All of them had a neutrophilic alveolitis with a higher median BAL cellularity than survivors (723 [IQR, 591 to 926] cells/μl versus 400 [IQR, 152 to 594] cells/μl, $P = 0.02$), whereas neutrophil and lymphocyte proportions were not statistically different from those of survivors (72% [IQR, 47 to 89] vs. 52% [35 to 74], $P = 0.25$, and 2% [IQR, 1 to 11] vs. 6% [IQR, 5 to 13], $P = 0.12$, respectively).

Concerning safety issues for the staff in charge, all procedures were alternatively performed by two trained pulmonologists, assisted by one out of three dedicated nurses. All of them carefully followed current guidelines for bronchoscopy in patients with COVID-19 (3) and remained COVID-19–free as assessed by a recent serological anti–SARS-CoV-2 immunoglobulin G testing (Architect; Abbott).

In conclusion, cytological analysis of BAL performed in patients with moderate to severe COVID-19–related ARDS typically shows a high cellularity, with neutrophilic alveolitis that could be linked to bacterial or fungal superinfections often observed in our population and/or be a hallmark of moderate to severe SARS-CoV-2–related ARDS itself. It may also reveal lymphocytosis, with a marked proportion of activated lymphocytes, especially when patients still carry the virus, at the early stage of the disease. In our series, although BAL was performed after a systematic noninvasive microbiological workup, it had a nonnegligible diagnostic yield and impact on medical decisions. BAL may therefore be considered as a complementary tool to noninvasive microbiological tests in selected patients with COVID-19–associated ARDS.

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Audrey Baron, M.D.
Mouna Hachem, M.D.
Jeanne Tran Van Nhieu, M.D., Ph.D.
Françoise Botterel, M.D., Ph.D.
Slim Fourati, M.D., Ph.D.
Guillaume Carteaux, M.D., Ph.D.
Nicolas De Prost, M.D., Ph.D.
Université Paris Est-Créteil
Créteil, France

and

AP-HP, Hôpitaux Universitaires Henri Mondor
Créteil, France

Bernard Maitre, M.D., Ph.D.
Université Paris Est-Créteil
Créteil, France

and

Hôpital Intercommunal de Créteil
Créteil, France

Armand Mekontso-Dessap, M.D., Ph.D.
Frédéric Schlemmer, M.D., Ph.D.*
Université Paris Est-Créteil
Créteil, France

and

AP-HP, Hôpitaux Universitaires Henri Mondor
Créteil, France

ORCID IDs: 0000-0002-4833-4320 (N.D.P.); 0000-0002-8061-1252 (B.M.); 0000-0003-2113-7113 (F.S.).

*Corresponding author (e-mail: frederic.schlemmer@aphp.fr).

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