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 bronchoscopy 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 (PaO₂/FiO₂), positive end-expiratory pressure (H₂O 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 | Overall | ≤10 d | >10 d | P Value* |
|-----------------------------|---------|-------|-------|----------|
| 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 | 16 (57) | 4 (37) | 12 (71) | 0.12     |
| Antifungal therapy at time of BAL | 15 (54) | 4 (36) | 11 (61) | 0.07     |
| 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 |
- 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 (80) | 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 antifungal therapy
  - 8 (29) | 4 (36) | 4 (24) | 0.67 |
- Modification of antibacterial 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 |

| Value*Overall | Overall | ≤10 d | >10 d | P Value* |
|---------------|---------|-------|-------|----------|

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 FIO2 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 days.
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 | Therapeutic Decision |
|---------------------------------------------|---------------------|----------------|--------------------|-------------|---------------------|
|                                            | Serum GM (Index)    | Tracheal Aspiration*: Culture/Aspergillus PCR† (Ct Value) | Bronchial Aspiration: Direct Examination/Culture | BAL: Culture | BAL: Aspergillus PCR (Ct Value)† | Direct Examination |            |
| 5/0                                         | Neg                 | Neg/Neg        | Neg/Neg            | Aspergillus sp (39) | Neg | No AFT |                     |
| 6/6                                         | Pos (0.8)           | Neg/Aspergillus sp (40) | Neg/C. albicans | — | Neg | colonization | AFT |
| 7/7                                         | Neg                 | Neg/Neg        | Pos/A. fumigatus | A. fumigatus | Neg | Putative IPA† | Start of AFT |
| 12/12                                       | Pos (0.7)           | Neg/Neg        | Pos/A. fumigatus | A. fumigatus | Neg | Putative IPA† | AFT |
| 15/15                                       | Neg                 | A. fumigatus/Neg | Neg/A. fumigatus & C. albicans | Neg | Neg | colonization | Withdrawal of AFT |
| 20/20                                       | Neg                 | Neg/Aspergillus sp (38) | Neg/A. fumigatus & C. albicans | C. albicans | Neg | Probable Aspergillus tracheobronchitis§ | AFT |
| 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                 | Neg/A. fumigatus & 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; Ct = 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.

Acknowledgment: The authors thank Nabila Ouidir Aissanou, Frédérique Boquet, Cécile Angebault, Paul Louis Woerther, and Vincent Fihman for their contribution through the cytological and microbiological analysis of BAL samples.

Author disclosures are available with the text of this letter at www.atsjournals.org.

References

1. Azoulay E, Mokart D, Lambert J, Lemiale V, Rabbat A, Kouatchet A, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med 2010;182:1038–1046.
2. Cracco C, Fartoukh M, Prodanovic H, Azoulay E, Chenivesse C, Lorut C, et al. Safety of performing fiberoptic bronchoscopy in critically ill hypoxemic patients with acute respiratory failure. Intensive Care Med 2013;39:45–52.
3. Lentz RJ, Colt H. Summarizing societal guidelines regarding bronchoscopy during the COVID-19 pandemic. Respirology 2020;25:574–577.
4. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One 2012;7:e35797.
5. Torrego A, Pajares V, Fernández-Arias C, Vera P, Mancebo J. Bronchoscopy in patients with COVID-19 with invasive mechanical ventilation: a single-center experience. Am J Respir Crit Care Med 2020;202:284–287.
6. Bruyneel M, Gabrovskva M, Rumpons P, Roman A, Claus M, Stevens E, et al. Bronchoscopy in COVID-19 intensive care unit patients. Respirology 2020;25:1313–1315.
7. Gao C, Cuttica M, Malin E, Argento AC, Wunderink R, Smith SB; NU COVID Investigators. Comparing nasopharyngeal and BAL SARS-CoV-2 assays in respiratory failure. Am J Respir Crit Care Med 2021;203:127–129.
8. Mondoni M, Sferrazza Papa GF, Rinaldo R, Faverio P, Marruchella A, D’Arcangelo F, et al. Utility and safety of bronchoscopy during the SARS-CoV-2 outbreak in Italy: a retrospective, multicentre study. Eur Respir J 2020;56:2002767.
9. Fowler AA, Hyers TM, Fisher BJ, Bechard DE, Centrom R, Webster RO. The adult respiratory distress syndrome: cell populations and soluble mediators in the air spaces of patients at high risk. Am Rev Respir Dis 1987;136:1225–1231.
10. Blot SI, Taccone FS, Van den Abeele A-M, Bulpa P, Meersseman W, Brusselaers N, et al. AspICU Study Investigators. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186:56–64.
11. Schauwvliege AFAD, Rijnders BJA, Philips N, Verweij R, Vanderbeke L, Van Tienhoven C, et al.; Dutch-Belgian Mycosis study group. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6:782–792.
12. Verweij PE, Rijnders BJA, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med 2020;46:1524–1535.