Role of bronchoscopy in critically ill patients managed in intermediate care units - indications and complications: A narrative review

Vincenzo G Menditto, Federico Mei, Benedetta Fabrizzi, Martina Bonifazi

ORCID number: Vincenzo G Menditto 0000-0001-6231-2251; Federico Mei 0000-0003-1887-5377; Benedetta Fabrizzi 0000-0003-2358-5470; Martina Bonifazi 0000-0003-2522-5583.

Author contributions: All authors wrote, read, and approved the final manuscript.

Conflict-of-interest statement: Authors certify that there is no conflict of interest related to the manuscript.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Specialty type: Critical care medicine

Country/Territory of origin: Italy

Flexible bronchoscopy (FB) has become a standard of care for the triad of inspection, sampling, and treatment in critical care patients. It is an invaluable tool for diagnostic and therapeutic purposes in critically ill patients in intensive care unit (ICU). Less is known about its role outside the ICU, particularly in the intermediate care unit (IMCU), a specialized environment, where an intermediate grade of intensive care and monitoring between standard care unit and ICU is provided. In the IMCU, the leading indications for a diagnostic work-up are: To visualize airway system/obstructions, perform investigations to detect respiratory infections, and identify potential sources of hemoptysis. The main procedures for therapeutic purposes are secretion aspiration, mucus plug removal to solve atelectasis (total or lobar), and blood aspiration during hemoptysis. The decision to perform FB might depend on the balance between potential benefits and risks due to frailty of critically ill patients. Serious adverse events related to FB are relatively uncommon, but they may be due to lack of expertise or appropriate precautions. Finally, nowadays, during dramatic recent coronavirus disease 2019 (COVID-19) pandemic, the exact role of FB in COVID-19 patients admitted to IMCU has yet to be clearly defined. Hence, we provide a concise review on the role of FB in an IMCU setting, focusing on its indications, technical aspects and complications.
Menditto VG et al. Bronchoscopy in critically ill patients

Key Words: Flexible bronchoscopy; Critically ill; Bronchoalveolar lavage; Indication; Complication; COVID-19

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

INTRODUCTION

Flexible bronchoscopy (FB) is a priceless tool for diagnostic and therapeutic purposes in critically ill patients in intensive care unit (ICU)[1,2]. Less is known about its role outside ICU, particularly in intermediate care unit setting (IMCU). In this setting too, FB is used both for diagnostic and therapeutic purposes. The leading indications in diagnostic work-up are: to visualize airway system/obstructions, to perform examinations to detect respiratory infections by means of bronchoalveolar lavage (BAL) and tissue sampling in specific circumstances, and to identify potential sources of hemoptysis. The main procedures for therapeutic purposes are aspiration of bronchial secretions, more frequently needed in patients with artificial airways, mucus plug removal to solve atelectasis (total or lobar) and blood aspiration during hemoptysis[3, 4]. Although FB is generally safe, complications may occur, particularly in critically ill patients, and thus, the risk-benefit profile of each procedure should be carefully evaluated.

Herein, we review the role of FB in critical patients, mainly focusing on the management of subgroups admitted to IMCU.

INDICATIONS

The common indications for FB in the ICU are the visualization of the trachea and main bronchi, restoring airway patency (especially in patients with artificial devices), managing hemoptysis and diagnostic sampling. In this setting, Olopade et al[5] found that FB was required in patients with acute respiratory failure, mainly as removing abundant secretions (50%), collecting samples (35%), assessment of the airways patency (7%), and hemoptysis (2%). However, in an IMCU setting, Korkmaz Ekren et al[6] described a cohort of 28 critical patients treated with non-invasive ventilation (NIV) in which the most frequent FB indications were: diagnostic approach for opportunistic infections (64.3%) or malignancy (14.3%) and therapeutic approach for airway obstruction (14.3%) or alveolar hemorrhage (14.3%).

INFECTIONS

In the ICU, FB with BAL in community-acquired pneumonia is used when antibiotic therapy fails or to investigate potential alternative diagnoses[3]. In critically ill non-intubated patients, Cracco et al[7] reported a diagnostic yield of BAL of 59%. A clinical
context, where FB appears particularly useful is immunocompromised patients, such as transplant recipients, those with hematologic malignancies, active cancer and receiving immunosuppressive therapy. The identification of infectious agent leads to ongoing treatments being modified in a relatively high percentage of patients, especially when pulmonary infiltrates are present[8-10]. The overall diagnostic yield of BAL in immunosuppressed patients ranges from 31% to 74%[11,12], and predictors of higher sensitivity are early intervention (within the first 4 d from the onset of symptoms) and the presence of radiologic findings consistent with an alveolar pattern, as compared to interstitial or nodular pattern[10]. According to recent guidelines, in cases of suspected pulmonary invasive aspergillosis, BAL galactomannan measurement is strongly recommended[13,14]. Moreover, BAL and transbronchial lung biopsy (TBLB) might be used for cytological analysis in case of suspected Pneumocystis jirovecii pneumonia (formerly known as pneumocystis carinii), acute eosinophilic pneumonia (BAL eosinophils > 25%) or tuberculosis[15]. BAL is particularly considered gold standard for diagnosis of Pneumocystis jirovecii, showing a sensitivity of 90%-98% in absence of previous antibiotic use for treatment or prophylaxis[3].

Finally, in cystic fibrosis, FB may allow for a more accurate diagnosis of lower respiratory tract infections, guiding the choice of antimicrobials in non-sputum producers[16]. However, according to the latest Cochrane systematic review on this topic[17], there is no clear evidence to support its routine use compared to standard practice, in which treatment choice is based on the results of oropharyngeal culture and clinical symptoms.

HEMOPHTYSIS/HEMORRHAGE

Hemoptysis is a challenging symptom associated with potentially life-threatening medical conditions[18]. FB plays a relevant role in this context, helping to diagnose the etiology, localize the site, and identify the source of the bleeding, essential for successful clinical management. Moreover, it allows for removal of clots, stopping active bleeding in certain cases (by means of bronchial blocker placement), and guiding angiographic embolization.

Mondoni et al[19] showed that the bleeding source detection rate of FB was higher in cases of moderate-severe hemoptysis rather than in mild ones, and when performed within 48 h from the last episode.

In massive hemoptysis, flexible FB can be unable to remove enough blood. In life-threatening hemoptysis, airways patency should be immediately preserved; in this context, rigid bronchoscopy (RB) or tracheal intubation under general anesthesia are better options in comparison with FB. Moreover, during RB, a Fogarty catheter or other bronchial blockers may be placed in order to stop active bleeding[18,20]. Alternatively, in cases of massive hemoptysis, FB can be useful for the selective main bronchial intubation to assure safe ventilation of non-bleeding site.

AIRWAY INSPECTION AND MANAGEMENT OF OBSTRUCTIONS

As previously stated, the role of FB in IMCU is essential to visualize airway system/obstructions and restore patency in different circumstances, such as atelectasis, lobar collapse due to mucoid plugs or inhalation injuries. Patients with artificial devices, such as tracheostomy cannula, frequently develop airway obstructions due to mucus plugs, secretions or clots. Bronchoscopic management of these cases includes removal of endobronchial material by means of suction or forceps. The overall success rate for the correction of acute atelectasis caused by airway obstruction due to mucus plugs is more than 70% in various reports[21,22].

Moreover, FB can be performed to evaluate tracheomalacia or tracheal stenosis after tracheostomy[23,24]. In selected, more complicated cases, RB may be required.

Aspiration of gastric contents can be an indication for FB with lavage in critical care patients, especially when the aspirate is predominantly particulate[25]. In this setting, a prompt FB can reduce inflammatory reaction, thus preventing atelectasis and reducing both the risk of infection and the development of acute respiratory distress syndrome[26].

FB can be useful for the visualization of the airways in case of thoracic trauma and suspected bronchial injury[27]. Bronchial fracture may occur in 3% of penetrating chest trauma and, in this context, FB might help to locate and estimate the degree of air leak[28].
Lastly, FB can be used for percutaneous dilatational tracheostomy, which is a rare but possible bedside procedure in critical care.

**TYPES OF BRONCHOSCOPIC PROCEDURES AND SEDATION**

There are two main types of bronchoscopes: RB and FB. The latter is more commonly employed in an IMCU setting but, in certain life-threatening conditions, RB is the preferred tool, as it allows for better airway control. These aforementioned conditions include massive hemoptysis, removal of large foreign bodies or resistant mucus plugs, dilatation, or stent procedures in the tracheobronchial tree. Over the last years, disposable systems, not containing fiber-optic cables but a distal camera connected to a re-usable screen, have been increasingly adopted in clinical practice, partly replacing traditional FB scopes (Figure 1). These combine quality of image with low manufacturing costs and allow for the reduction of scope downtime by eliminating the need for disinfection between procedures and potentially decreasing the risk of cross-contamination and infectious outbreaks[2].

Patients admitted to an IMCU are usually at higher risk of complications because hypoxemia, hemodynamically instability, and at higher risk of bleeding because of thrombocytopenia or anticoagulant/antithrombotic treatment. Therefore, the risk-benefit profile of each procedure should be carefully evaluated, as well as the choice of the proper type of sedation, which is crucial for a successful outcome. According to recent international guidelines[3,29], all bronchoscopies should be performed under topical anesthesia by means of nasal nebulized lidocaine (100 mg) in association with conscious or deep sedation. Intravenous sedation should be offered to patients undergoing bronchoscopy to decrease anxiety and discomfort, improve pain control and produce anterograde amnesia. The depth of sedation should be tailored individually and according to the complexity of procedure; advanced diagnostic and therapeutic bronchoscopies require deep sedation and an anesthesiologist’s assistance is highly recommended. The most common medications used for sedation and pain control are benzodiazepines (midazolam, up to 5 mg), opioids (fentanyl, up to 0.5-20 μg/kg) and propofol[30]. The combination of midazolam and opioids causes a synergistic effect on patients’ pain tolerance, as well as on pain control and suppression of cough, thus improving tolerance to FB in difficult situations, including patients requiring NIV. NIV provides adequate gas exchange, reducing the workload of breathing during FB, and can be used both in severely hypoxemic and hypercapnic patients by means of different interfaces (Figure 2)[31].

Here, a brief description of the most common bronchoscopic procedures performed in IMCUs is provided.

**SAMPLING PROCEDURES**

BAL is a safe and minimally invasive bronchoscopic sampling method, indicated for several lung diseases (e.g., immune-mediated, inflammatory, and infectious diseases). It can provide specimens for cytological and microbiological exams. Due to its excellent safety profile, BAL can be performed in critically ill patients, while carefully monitoring vital parameters. A complete airway inspection should precede BAL execution, which, in turn, should precede any biopsies[15,31,32]. The bronchoscope should advance as far as possible to the complete occlusion of the bronchial lumen of a third or fourth bronchial subsegment, in a wedged position. 60-180 mL of room temperature sterile saline is used, divided into 3 fractions, and introduced through the suction channel of the bronchoscope. It is then withdrawn by suction, aiming to retrieve as much fluid as possible, without causing airway collapse. The BAL fluid is subsequently stained and cultured for pathogens.

**BRONCHIAL WASHING**

Bronchial washing (BW) consists of the instillation and subsequent aspiration of small amounts of saline solution (usually 20-50 mL) mixed with bronchial secretions, into a specific bronchial trap. It may be useful to assess the microbiology of central airway secretions. A major limitation of this technique is the high risk of contamination with non-pathological organisms from upper airways that are not indicative of a real
TISSUE SAMPLING TECHNIQUES

Patients admitted to IMCUs might occasionally present pulmonary consolidations and/or nodules. Tissue acquisition can be indicated in selected cases, and forceps and needles are the most common sampling tools adopted by bronchoscopists.

Endobronchial biopsy is recommended for the diagnosis of visible endobronchial lesions; forceps should be opened outside the distal end of the operating channel and pushed against the lesion. The tip of the forceps is then closed and extracted from the operating channel of the bronchoscope, and the specimen is then placed in formalin solution. Forceps biopsy showed a sensitivity of 72%-100% in the detection of TB granulomas (endobronchial TB)[35] and may be useful in ruling out malignancies or sarcoidosis, particularly in the latter, when associated with TBLB. TBLB is commonly used in diagnostic work-up of malignancy, diffuse lung disease and infection, when the lesion cannot be directly accessed with a bronchoscope. It is wedged into the bronchus pertaining to the anatomical site of the lesion, and the closed forceps are pushed into the peripheral area of the lung, opened at 5-6 mm from the lesion and then closed to collect a sample. TBLB is usually performed under fluoroscopy guidance, even though innovative navigation systems have been recently adopted in bronchial infection[33-36].
clinical practice (i.e. electromagnetic navigation bronchoscopy, radial probe ultrasounds, virtual bronchoscopy).

Needle aspiration sampling techniques are also largely employed, especially for the diagnosis of peripheral lesions as well as in the case of hilar/mediastinal lymph nodes or masses[37,38]. A thin retractable needle (21-gauge for cytology sampling and 19-gauge for histology) is inserted into the working channel of the bronchoscope, and pushed into lesions through the tracheobronchial wall, blindly (conventional - cTBNA) or under endoscopic ultrasound guidance (EBUS-TBNA)[38].

AIRWAY OBSTRUCTION MANAGEMENT

Central airway obstruction (CAO) may occur in an IMCU setting. CAO is defined as the occlusion of 50% or more of tracheal or mainstem bronchial lumen and may occur either in a patient with malignant (lung cancer or metastases from extra thoracic malignancies) or benign conditions (inflammation, necrotizing tracheobronchial infection, mucus plug blockage, simple or complex post-tracheostomy or intubation stenosis).

Interventional pulmonology plays a major role in this context. Several ablative techniques are currently available and include ‘immediate’ or ‘delayed’ procedures based on the time expected to restore airway patency. In case of critical lesions, it is mandatory to promptly restore ventilation through ‘immediate’ techniques, whereas ‘delayed’ approaches, with a prolonged effect, should be reserved for a non-emergency setting, according to clinical and prognostic factors. Recent data has confirmed that almost every technique, when carried out by experienced hands and according to specific indications, is highly effective in restoring airway patency, with a valuable risk-benefit profile. In any case, deep sedation and endotracheal intubation through RB are required for a safer and effective management.

‘Immediate’ interventions include mechanical debulking, laser, electrocautery, and argon plasma coagulation. The most common ‘delayed’ techniques, requiring a staged procedure, are brachytherapy and photodynamic therapy[39]. Cryotherapy may be included in both categories as, according to the technology employed, it can result in either an immediate or delayed effect, called cryorecanalization and freeze–thaw cryotherapy respectively. All these techniques can be combined as part of a multimodal approach, aimed both at improving therapeutic success rates and reducing the risk of complications.

Once airway patency has been restored, a stent placement can be considered in selected patients with high recurrence risk. Over the last years, more and more stents have become available, including tailored stents and metallic Y-shaped stents. However, complications after stent placement are not uncommon and may include clogging of the stent with secretions, ingrowth of granulation or tumor tissue at the ends of the stent, migration, or fracture of the mesh structure of the stent. As a result, proper artificial airway management includes securing the tracheal tube, monitoring tube position, maintaining patency, and appropriate regulation of cuff pressure.

BRONCHOSCOPY IN TIMES OF CORONAVIRUS DISEASE

Data on the risk-benefit profile of FB in patients with coronavirus disease 2019 (COVID-19) are still limited and controversial[30,40,41]. In patients with suspected COVID-19, FB seems to slightly increase the sensitivity of a molecular diagnosis compared to that of nasopharyngeal swabs (NPS)[41]. However, in cases with inconsistent thoracic imaging and negative NSP, BAL[42,43] presents a further limited role in the diagnosis of COVID-19. Moreover, FB generates aerosols and may increase the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission among healthcare workers[29,40].

In a non-ICU setting, a multicenter retrospective Italian study[43] reported the results of 108 FB, of which 75% were performed during oxygen supplementation, 12% while patients were breathing room air and 3% during NIV. In 72%, FB was performed to diagnose SARS-CoV-2 infection in patients with clinical and radiological suspicion of COVID-19 pneumonia and negative NPS, with a reported 57.7% (45 out of 78 patients) definite diagnosis of COVID-19 pneumonia. In 28% of cases, FB was performed on patients with a confirmed diagnosis of COVID-19 affected by the following clinical conditions: suspected concomitant lower respiratory tract infections, obstructive atelectasis, suspected tracheal intubation-related complications,
tracheostomy complications and severe hemoptysis. Moreover, the authors reported that healthcare workers did not acquire any infections after endoscopic procedures, performed according to World Health Organization guidelines on airborne precautions for aerosol-generating procedures [44].

In another Italian cohort [45] of 131 hospitalized patients with moderate disease (mostly in internal medicine wards), indications for FB were: 65% suspected SARS-CoV-2 infection, 13% alternative diagnosis (i.e. hemoptysis or lung consolidations), 20% suspected superinfections, and 2% lung atelectasis. A confirmed diagnosis of SARS-CoV-2 was reported in 37% of patients with double-negative NPS. Concordance of BAL and NPS was overall high (98.9%, P > 0.0001), as confirmed by Geri et al. [46] as well (97.5% overall agreement with a moderate Cohen’s k = 0.487). In particular, patients with moderate disease who underwent FB for a suspected SARS-CoV-2 infection presented a higher number of computed tomography (CT) alterations than patients with other indications. Moreover, since most of patients with moderate disease underwent FB several days after the development of symptoms, consequently BAL diagnostic yield resulted gradually decreased from symptom onset.

So far, scientific pulmonology societies [29,41] have issued a general recommendation against the use of FB in non-intubated SARS-CoV-2 suspected patients. However, it was postulated that the benefits of FB with BAL would outweigh side effects for patients and risks for the healthcare team in the case of: (1) at least one negative NPS; (2) instability from a respiratory point of view; and (3) atypical CT scan suggestive of an alternative diagnosis [47].

FB may also be helpful in intubated patients during the course of COVID-19 pneumonia to detect superinfections and to restore airway patency from obstructions secondary to thick distal secretions, particularly common after prolonged mechanical ventilation, and/or clots, due to anticoagulation drugs [48].

**COMPLICATIONS**

Overall, data from literature on FB safety in an ICU setting reported a reassuring profile, with a complication and mortality rate of 1.1% and 0.02%, respectively [49]. Predictors of complications include “intrinsic”, non-modifiable, patient conditions (age, presence of respiratory failure, severity of comorbidities, concomitant medications and coagulation abnormalities) and procedure-related factors (type of procedure, duration, sedation and operator’s experience) [7,49]. In this context, a standardized protocol for FB execution in ICU patients is highly recommended in order to guide the decision-making process on indications and timing, to estimate individualized risks and to arrange in advance proper interventions.

**HYPOXEMIA**

Transient hypoxemia is the most common adverse event, being the result of a combination of alveolar collapse and depletion of intra-alveolar oxygen due to frequent suctioning and massive washing of the alveoli during BAL. Conversely, hypercapnia is usually the expression of hypoventilation caused by airway obstruction. Since most patients admitted to ICUs with acute respiratory failure are on oxygen supplementation or NIV, escalation in ventilatory support is one of the most common concern in the decision-making process, but in experienced hands and with adequate precautions, FB still has an acceptable safety profile in this context [50].

**BLEEDING**

Although patients admitted to ICUs usually present a baseline high risk of hemorrhage due to concomitant comorbidities and medications (antiplatelets, anticoagulants, chemotherapy), the post-bronchoscopy bleeding rate is relatively low: 0.12% for FB with BAL and 3%-5% for TBLB or EBUS-TBNA [1]. To reduce the likelihood of this potential complication, it is crucial to optimize platelet count, prothrombin time and thromboplastin time values before FB and to effectively manage any drug that might influence coagulation parameters (warfarin, direct anti-coagulants, antiplatelet agents).
PNEUMOTHORAX

Pneumothorax rarely occurs during FB (0.1%) or TBLB (0.4%) [49]. Even though pneumothorax mostly happens within a few minutes after procedure, in a substantial minority of cases (approximately 40%) it can be delayed, requiring a careful monitoring of clinical parameters, particularly in patients under NIV.

In this context, in addition to a chest X-ray, a bedside lung ultrasound may be helpful for detecting pneumothorax with an extremely high diagnostic accuracy [51].

OTHERS

Hypoxemia occurring during FB may cause an increase in cardiac workload, with elevations of heart rate (approximately 40% above baseline), blood pressure (a rise of 30% above baseline) and cardiac index (approximately 17%-32% above baseline). Despite this, major arrhythmias, as well as myocardial infarction, are rare events during FB.

Iatrogenic trauma to airways and bronchospasm have also been occasionally reported whereas the onset of fever is relatively common, particularly after BAL (13%) or bronchial washing [52].

CONCLUSION

Future research directions and conclusions

In the past decades, interventional pulmonology has experienced a remarkable growth in available technology and equipment, as well as clinical and translational research efforts focused on patient-centered outcomes. Recent studies highlight the feasibility of using metagenomic sequencing on BAL for the microbiologic diagnosis of adults with severe community-acquired pneumonia [53, 54]. Moreover, biomarkers and cytokines in BAL fluid may have diagnostic benefits for certain diseases in critically ill patients in the present and near future. Moreover, in COVID-19 pandemic, FB may be crucial to assess and understand the inflammatory status at broncho-alveolar level during different stages of infection [55-57].

The role of FB in ICU setting has not yet fully established, but data from literature suggest that it is an essential tool in a not negligible proportion of pulmonary conditions.

However, standardized protocols on procedure execution as well as decision-making algorithms are currently lacking, leading to hugely different approaches in clinical practice, mainly depending on local sources and expertise availability.

As this field continues to push its boundaries, it is imperative to establish evidence and best practice guidelines.

REFERENCES

1 Ergan B, Nava S. The use of bronchoscopy in critically ill patients: considerations and complications. *Expert Rev Respir Med* 2018; 12: 651-663 [PMID: 29958019 DOI: 10.1080/17476348.2018.1494576]
2 Kabadayi S, Bellamy MC. Bronchoscopy in critical care. *BJA Educat* 2017; 17: 48-56 [DOI: 10.1093/bjaed/mkw040]
3 Du Rand IA, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalid S, Mandler S, Martin J, Mills J, Navani N, Rahman NM, Wrightson JM, Munavvar M; British Thoracic Society Bronchoscopy Guideline Group. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax* 2013; 68 Suppl 1: i1-i44 [PMID: 23860341 DOI: 10.1136/thoraxjnl-2013-203618]
4 Liebler JM, Markin CJ. Fiberoptic bronchoscopy for diagnosis and treatment. *Crit Care Clin* 2000; 16: 83-100 [PMID: 10650501 DOI: 10.1016/s0749-0704(05)70098-1]
5 Olopade CO, Prakash UB. Bronchoscopy in the critical-care unit. *Mayo Clin Proc* 1989; 64: 1255-1263 [PMID: 2687588 DOI: 10.1016/s0025-6196(12)61288-9]
6 Korkmaz Ekren P, Basarik Aydogan B, Gurgun A, Tasbakan MS, Bacakoglu F, Nava S. Can fiberoptic bronchoscopy be applied to critically ill patients treated with noninvasive ventilation for acute respiratory distress syndrome? *BMC Pulm Med* 2016; 16: 89 [PMID: 27245054 DOI: 10.1186/s12890-016-0236-y]
7 Cracco C, Fartoukh M, Prodanovic H, Azoulay E, Chenivesse C, Lorut C, Bedeneau G, Bui HN, Taille C, Brochard L, Demoule A, Maitre B. Safety of performing fiberoptic bronchoscopy in...
critically ill hypoxic patients with acute respiratory failure. *Intensive Care Med* 2013; 39: 45-52 [PMID: 23070123 DOI: 10.1007/s00134-012-2687-9]

8 Peikert T, Rana S, Edell ES. Safety, diagnostic yield, and therapeutic implications of flexible bronchoscopy in patients with febrile neutropenia and pulmonary infiltrates. *Mayo Clin Proc* 2005; 80: 1414-1420 [PMID: 16295020 DOI: 10.4065/80.11.1414]

9 Shannon VR, Andersson BS, Lei X, Champlin RE, Kontoyiannis DP. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2010; 45: 647-655 [PMID: 19684637 DOI: 10.1038/bmt.2009.203]

10 Brownback KR, Simpson SQ. Association of bronchoalveolar lavage yield with chest computed tomography findings and symptoms in immunocompromised patients. *Ann Thorac Med* 2013; 8: 153-159 [PMID: 23922610 DOI: 10.4103/1817-1737.114302]

11 Ramírez P, Valencia M, Torres A. Bronchoalveolar lavage to diagnose respiratory infections. *Semin Respir Crit Care Med* 2007; 28: 525-533 [PMID: 17975780 DOI: 10.1055/s-2007-991524]

12 Sanchez JF, Ghamande SA, Miduri JK, Arroliga AC. Invasive diagnostic strategies in immunosuppressed patients with acute respiratory distress syndrome. *Clin Chest Med* 2014; 35: 697-712 [PMID: 25453419 DOI: 10.1016/j.ccm.2014.08.008]

13 Ullmann AJ, Aguado JM, Arikian-Akdagli S, Denning DW, Groll AH, Lagrou K, Lass-Flörl C, Lewis RE, Munoz P, Verweij PE, Warris A, Ader F, Akova M, Arendrup MC, Barnes RA, Beigelman-Aubry C, Birtz S, Bouza E, Brüggemann RJM, Buchheidt D, Cadranel J, Castagnola E, Chakrabarti A, Cuenca-Estrella M, Dimopoulos G, Fortun J, Gangneux JP, Garbino J, Heinz WJ, Herbrecht R, Heussel CP, Kibbler CC, Klimko N, Kullberg BJ, Lange C, Lehnhuber T, Löffler J, Lortholary O, Maertens J, Marchetti O, Meis JF, Pagano L, Rottoli P, Saltini C, Selman M, Strange C, Wood B; American Thoracic Society Committee on BAL in Interstitial Lung Disease. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012; 185: 1004-1014 [PMID: 22550210 DOI: 10.1164/rccm.201202-0320ST]

14 Aridgides D, Dessaint J, Atkins G, Carroll J, Ashare A. Safety of research bronchoscopy with BAL in stable adult patients with cystic fibrosis. *PLoS One* 2021; 16: e0245696 [PMID: 33481845 DOI: 10.1371/journal.pone.0245696]

15 Jain K, Wainwright C, Smyth AR. Bronchoscopy-guided antimicrobial therapy for cystic fibrosis. *Cochrane Database Syst Rev* 2013; CD009530 [PMID: 24363033 DOI: 10.1002/14651858.CD009530.ppub2]

16 Botnick W, Brown H. Endobronchial urokinase for dissolution of massive clot following transbronchial biopsy. *Chest* 1994; 105: 953-954 [PMID: 8131576 DOI: 10.1378/chest.105.3.953]

17 Turner JS, Willcox PA, Hayhurst MD, Potgieter PD. Fiberoptic bronchoscopy in the intensive care unit—a prospective study of 147 procedures in 107 patients. *Crit Care Med* 1994; 22: 259-264 [PMID: 8306685 DOI: 10.1097/00003246-199402000-00017]

18 Kreider ME, Lipson DA. Bronchoscopy for atelectasis in the ICU: a case report and review of the literature. *Chest* 2003; 124: 344-350 [PMID: 12853543 DOI: 10.1378/chest.124.1.344]

19 Tsakiridis K, Durwiche K, Visouli AN, Zarogoulidis K, Machairiotis N, Christofis C, Stylianaki A, Katsikogiannis N, Mpakas A, Courcoutsakis N, Zarogoulidis K. Management of complex benign post-tracheostomy tracheal stenosis with bronchoscopic insertion of silicon tracheal stents, in patients with failed or contraindicated surgical reconstruction of the trachea. *J Thorac Dis* 2012; 4 Suppl 1: 32-40 [PMID: 23304439 DOI: 10.3978/j.issn.2072-1439.2012.0602]

20 Noppen M, Stratagós G, Amjad K, De Weerdt S, D’Haese J, Meysman M, Vincken W. Stenting allows weaning and extubation in ventilator- or tracheostomy dependency secondary to benign airway disease. *Respir Med* 2007; 101: 139-145 [PMID: 16709452 DOI: 10.1016/j.rmed.2006.03.037]

21 Raghavendra N, Nemzek J, Napolitano LM, Knight PR. Aspiration-induced lung injury. *Crit Care Med* 2011; 39: 818-826 [PMID: 21263315 DOI: 10.1097/CCM.0b013e31820a856b]

22 Marik PE. Aspiration pneumonia and aspiration pneumonia. *N Engl J Med* 2001; 344: 665-671 [PMID: 11228282 DOI: 10.1056/NEJM200103013440908]

23 Martin-Löeches I, Artigas A, Gordo F, Añón JM, Rodríguez A, Blanch L, Cuiat J. [Current status of fiberoptic bronchoscopy in intensive care medicine]. *Med Intensiva* 2012; 36: 644-649 [PMID:
Zhao Z, Zhang T, Yin X, Zhao J, Li X, Zhou Y. Update on the diagnosis and treatment of tracheal and bronchial injury. *J Thorac Dis* 2017; 9: E50-E56 [PMID: 28203437 DOI: 10.21037/jtd.2017.01.19]

Wahidi MM, Shojaee S, Lamb CR, Ost D, Maldonado F, Eapen G, Caroff DA, Stevens MP, Ouellerte DR, Lilly C, Gardner DD, Glisinski K, Pennington K, Alalawi R. The Use of Bronchoscopy During the Coronavirus Disease 2019 Pandemic. CHEST/AABIP Guideline and Expert Panel Report. *Chest* 2020; 158: 1268-1281 [PMID: 32361152 DOI: 10.1016/j.chest.2020.04.036]

Esquinas A, Zuil M, Scala R, Chiner E. Bronchoscopy during non-invasive mechanical ventilation: a review of techniques and procedures. *Arch Bronconeumol* 2013; 49: 105-112 [PMID: 22819004 DOI: 10.1016/j.arbres.2012.05.008]

Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Jokoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldán I, Selman M, Travis WD, Walsh S, Wilson KC; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018; 198: e44-e68 [PMID: 30168753 DOI: 10.1164/rccm.201807-1255ST]

Baughman RP. Technical aspects of bronchoalveolar lavage: recommendations for a standard procedure. *Semin Respir Crit Care Med* 2007; 28: 475-485 [PMID: 17975775 DOI: 10.1055/s-2007-993526]

Lee HS, Kwon SY, Kim DK, Yoon HI, Lee SM, Lee JH, Lee CT, Chung HS, Han SK, Shim YS, Yim JJ. Bronchial washing yield before and after forceps biopsy in patients with endoscopically visible lung cancers. *Respirology* 2007; 12: 277-282 [PMID: 17298463 DOI: 10.1111/j.1440-1843.2006.01001.x]

van der Drift MA, van der Wilt GJ, Thunnissen FB, Janssen JP. A prospective study of the timing and cost-effectiveness of bronchial washing during bronchoscopy for pulmonary malignant tumors. *Chest* 2005; 128: 394-400 [PMID: 16002962 DOI: 10.1378/chest.128.1.394]

Mondoni M, Repossi A, Carlucci P, Centanni S, Sotgiu G. Bronchoscopic techniques in the management of patients with tuberculosis. *Int J Infect Dis* 2017; 64: 27-37 [PMID: 28864395 DOI: 10.1016/j.ijid.2017.08.008]

Jo YS, Park JH, Lee JK, Heo EY, Chung HS, Kim DK. Discordance between MTB/RIF and Real-Time Tuberculosts-Specific Polymerase Chain Reaction Assay in Bronchial Washing Specimen and Its Clinical Implications. *PLoS One* 2016; 11: e0164923 [PMID: 27760181 DOI: 10.1371/journal.pone.0164923]

Trisolini R, Patelli M, Ceron L, Gasparini S. Transbronchial needle aspiration. *Monaldi Arch Chest Dis* 2011; 75: 44-49 [PMID: 21626993 DOI: 10.4081/monaldi.2011.240]

Gasparini S. Bronchoscopic biopsy techniques in the diagnosis and staging of lung cancer. *Monaldi Arch Chest Dis* 1997; 52: 392-396 [PMID: 9401374]

Gasparini S, Bonifazi M. Management of endobronchial tumors. *Curr Opin Pulm Med* 2016; 22: 245-251 [PMID: 26950887 DOI: 10.1097/MCP.0000000000000259]

Luo F, Darwiche K, Singh S, Torrego A, Steinfort DP, Gasparini S, Liu D, Zhang W, Fernandez-Bussy S, Herth FFJ, Shah PL. Performing Bronchoscopy in Times of the COVID-19 Pandemic: Practice Statement from an International Expert Panel. *Respiration* 2020; 99: 417-422 [PMID: 32344422 DOI: 10.1159/000507898]

Wahidi MM, Lamb C, Murgu S, Musani A, Shojaee S, Sachdeva A, Maldonado F, Mahmood K, Kinsey M, Sethi S, Mahajan A, Majid A, Keyes C, Alraies AH, Sung A, Hsia D, Eapen G. American Association for Bronchology and Intervenional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients With Suspected or Confirmed COVID-19 Infection. *J Bronchology Interv Pulmonol* 2020; 27: e52-e54 [PMID: 32195687 DOI: 10.1097/LBR.0000000000000681]

Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020; 323: 1843-1844 [PMID: 32159775 DOI: 10.1001/jama.2020.3786]

Mondoni M, Sferrazza Papa GF, Rinaldo R, Faverio P, Marrachella A, D’Arcangelo F, Pesce A, Pasini S, Henchi S, Cipolla G, Tarantini F, Giuliani L, Di Marco F, Saracino L, Tomasselli S, Corsi A, Gasparini S, Bonifazi M, Zuccatoasta L, Saderi L, Pellegrino G, Davi M, Carlucci P, Centanni S, Sotgiu G. Utility and safety of bronchoscopy since the SARS-CoV-2 outbreak in Italy: a retrospective, multicentre study. *Eur Respir J* 2020; 56 [PMID: 32859682 DOI: 10.1183/13993003.02767-2020]

World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected; WHO/2019-nCoV/IPC/2020.3. [cited 18 March 2020]. Available from: http://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200212

Patruno F, Albera C, Belloccia M, Foci V, Gavelli F, Castello LM, Bellan M, Sainaghi PP, Airoldi C, Balbo PE, Solidoro P. SARS-CoV-2 Detection on Bronchoscoevlar Lavage: An Italian Multicenter experience. *Respiration* 2020; 99: 970-978 [PMID: 33075793 DOI: 10.1159/000519164]
Confalonieri P, Ruaro B, D’Agaro P, Gasparini S, Confalonieri M. Limited role for bronchoalveolar lavage to exclude COVID-19 after negative upper respiratory tract swabs: a multicentre study. *Eur Respir J* 2020; 56 [PMID: 32764117] DOI: 10.1183/13993003.01733-2020

Taton O, Papeux E, Bondue B, Knoop C, Van Laethem S, Bauler A, Marty M, Montesinos I, Delforge ML, Elmaouhab K, Leduc D. Role of the Bronchoalveolar Lavage in Noncritically Ill Patients during the SARS-CoV-2 Epidemic. *Pulm Med* 2020; [PMID: 33381313] DOI: 10.1155/2020/9012187

Chang SH, Jiang I, Kon ZN, Williams DM, Geraci TC, Smith DF, Cerfolio RJ, Zervos M, Bizekis C. Safety and Efficacy of Bronchoscopy in Critically Ill Patients With Coronavirus Disease 2019. *Chest* 2021; 159: 870-872 [PMID: 33039461] DOI: 10.1016/j.chest.2020.09.263

Taton O, Papleux E, Bondue B, Knoop C, Van Laethem S, Bauler A, Marty M, Montesinos I, Delforge ML, Elmaouhab K, Leduc D. Role of the Bronchoalveolar Lavage in Noncritically Ill Patients during the SARS-CoV-2 Epidemic. *Pulm Med* 2020; [PMID: 33381313] DOI: 10.1155/2020/9012187

Facciolongo N, Patelli M, Gasparini S, Lazzari Agli L, Salio M, Simonassi C, Del Prato B, Zanoni P. Incidence of complications in bronchoscopy. Multicentre prospective study of 20,986 bronchoscopies. *Monaldi Arch Chest Dis* 2009; 71: 8-14 [PMID: 19522159] DOI: 10.4081/monaldi.2009.370

Bernasconi M, Koegeleen CFN, Koutsokera A, Ogna A, Casutt A, Nicod L, Lovis A. Iatrogenic bleeding during flexible bronchoscopy: risk factors, prophylactic measures and management. *ERJ Open Res* 2017; 3 [PMID: 28656131] DOI: 10.1183/23120541.00084-2016

Banka R, Skaarup S, Mercer R, Laursen C. Thoracic ultrasound: A key tool beyond procedure guidance. In: Maskell NA, Laursen CB, Lee YCG, Rahman NM, editors. Pleural Disease (ERS Monograph). European Respiratory Society: Sheffield, UK, 2020: 73-89

Um SW, Choi CM, Lee CT, Kim YW, Han SK, Shim YS, Yoo CG. Prospective analysis of clinical characteristics and risk factors of postbronchoscopy fever. *Chest* 2004; 125: 945-952 [PMID: 15006953] DOI: 10.1378/chest.125.3.945

Sinner PJ, Miller S, Carroll KC. Understanding the Promises and Hurdles of Metagenomic Next-Generation Sequencing as a Diagnostic Tool for Infectious Diseases. *Clin Infect Dis* 2018; 66: 778-788 [PMID: 29040428] DOI: 10.1093/cid/cix388

Wu X, Li Y, Zhang M, Li M, Zhang R, Lu X, Gao W, Li Q, Xia Y, Pan P. Etiology of Severe Community-Acquired Pneumonia in Adults Based on Metagenomic Next-Generation Sequencing: A Prospective Multicenter Study. *Infect Dis Ther* 2020; 9: 1003-1015 [PMID: 33198751] DOI: 10.1007/s40121-020-00353-z

Pandolfi L, Fossali T, Frangipane V, Bozzini S, Morosini M, D’Amato M, Lettieri S, Urtis M, Di Toro A, Saracino L, Percivalle E, Tomaselli S, Cavagna L, Cova E, Mojo F, Bergomi P, Ottolina D, Lilleri D, Corsico AG, Arbustini E, Colombo R, Meloni F. Broncho-alveolar lavage in COVID-19 patients: a correlation with clinical outcome. *BMC Pulm Med* 2020; 20: 301 [PMID: 33198751] DOI: 10.1186/s12890-020-01343-z

Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, Cheng L, Li J, Wang X, Wang F, Liu L, Amit I, Zhang S, Zhang Z. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med* 2020; 26: 842-844 [PMID: 32398875] DOI: 10.1038/s41591-020-0901-9

Middleton EA, He XY, Denorme F, Campbell RA, Ng D, Salvatore SP, Mostyka M, Baxter-Stoltzfus A, Boreczak AC, Loda M, Cody MJ, Manne BK, Portier I, Harris ES, Petrey AC, Beswick EJ, Caulin AF, Iovino A, Abegglen LM, Weyrich AS, Rondina MT, Egeland M, Schiffman JD, Yost CC. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood* 2020; 136: 1169-1179 [PMID: 32597958] DOI: 10.1182/blood.2020007008
