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MINIREVIEWS

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

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Abstract

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.

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Core Tip: Less is known about the role of flexible bronchoscopy (FB) outside the intensive care unit, in particular in the intermediate care unit setting (IMCU). Here, we provide a concise review on the role of FB in IMCU settings, focusing on its indications, technical aspects and complications with a particular attention of its recent use in coronavirus disease 2019 patients. We reviewed the main diagnostic indications, such as viewing airway system/obstructions, detecting respiratory infections, and main therapeutic indications, such as secretion removal (toilet bronchoscopy) and manage hemoptysis.

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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.

HEMOPTYSIS/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 obstruc-tions 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

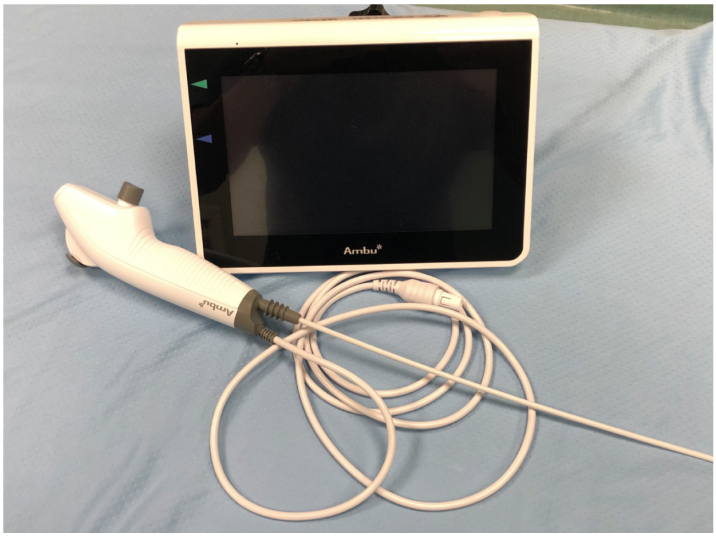

Figure 1 Disposable bronchoscopy.

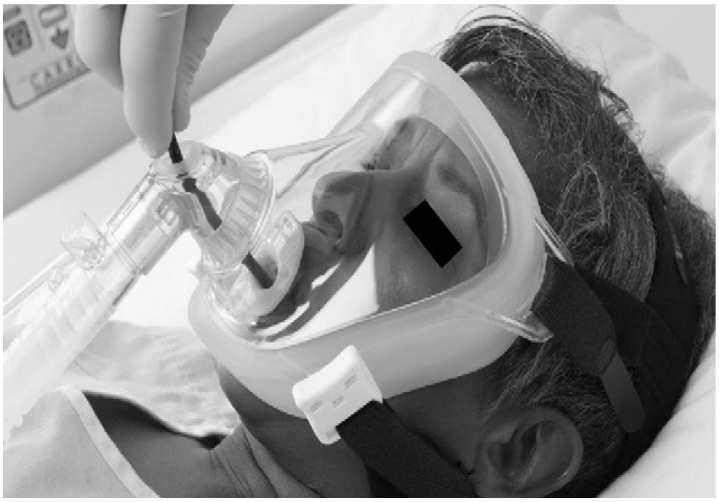

Figure 2 Face mask for non-invasive mechanical ventilation with diaphragm for the entry of the bronchoscope; oral insertion through the mouthpiece.

bronchial infection[33-36].

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

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 multi-modal 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 ICMU 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 IMCU 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 IMCUs 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 IMCUs 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, antiplatelets 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 ICMU 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.

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