Infectious complications following bronchoscopy: does sedation play a role?

Abstract
Bronchoscopy is an invasive procedure, which could favor infectious complications. Deep sedation may increase this risk. In this article, the available current evidence and the pathogenic mechanisms involved are analyzed.

Keywords: bronchoscopy, sedation, deep sedation, bronchoaspirate, microbioma, pneumonia, propofol

Introduction
Flexible bronchoscopy (FB) is a very useful and safe technique,1 with a low complication rate,2-6 but usually poorly tolerated by the patient.7-9 During bronchoscopy there may be passage of the oropharyngeal content into the infra-glottic airway, due to the introduction of the bronchoscope through the vocal cords, eliminating one of the defensive barriers to avoid bronchoaspiration, this being one of the possible mechanisms of infectious complications post-bronchoscopy,10,11

International guidelines recommend offering sedation to all patients, since it improves the performance and tolerance of bronchoscopy,12-14 but depression of consciousness may favor the aspiration of oropharyngeal content to the airway, with consequent contamination of the bronchoscopic sample, and eventually, the development of post-bronchoscopy pneumonia.15-21

Discussion
The prevalence of post-bronchoscopy fever is variable (from 5 to 68%), including both childhood and adult population, and different bronchoscopic techniques (bronchoalveolar lavage (BAL), transbronchial needle aspiration; BAS, bronchoaspirate; EBUS, endobronchial ultrasound; NSCLC, non-small cell lung cancer)

Infectious complications, such as pneumonia and pneumococcal sepsis,26,27 sepsis due to Gram-negative bacillus,28 pneumococcal meningitis,29 post-transbronchial needle aspiration (TBNA) purulent pericarditis,30 a possible case of St. viridans endocarditis in an HIV male with mitral prolapse,31 brain abscess due to viridans 1 month after a bronchoscopy for pneumonia.32

Epstein et al.,33 after a case of post-TBNA polybacterial pericarditis, systematically cultured the subcarinal-TBNA of 7 consecutive patients, and in all they found microorganisms of the oropharynx, identifying the subcarinal TBNA as a possible cause of purulent pericarditis, suggesting that the needle becomes contaminated when it passes through the working channel of the bronchoscope.29

Probably, not all types of endoscopy have the same risk of bacteremia.33 In a study of 555 people aged 60 years and over, who underwent bronchoscopy, gastroscopy and cystoscopy, antibiotics (ATB) were prophylactically administered in an alternative manner to patients; bacteremia was identified by blood cultures. In the 74 patients undergoing bronchoscopy, 1 blood culture was positive in the control group and none in the ATB group (37 patients, <5%), while the percentage for gastroscopies was 9.8% (0/130 ATB group and 12/132 control group), and for cystoscopies it was 27.5% (1/88 in the ATB group and 25/91 in the control group).33

However, despite these prior published reports, the evidence on post-bronchoscopy infections is inconsistent. It is not common to see patients who develop infections after a bronchoscopy, and several studies exceptionally find positive blood cultures.22,24,34 Dürschmied describes 2.9% transient bacteremia post-bronchoscopy with biopsies.35

Yigla et al.,37 describes 6.5% of bacteremia in a sample of 200 patients (14.5% of children) without infection or previous antibiotics, to whom different procedures were performed (BAL, brushing, bronchial biopsy, transbronchial biopsy), finding episodes of bacteremia that occur without damage of the mucosa.38 Picard et al.39 describes an elevated incidence of fever (48%) in immunocompetent children, being more frequent if BAL is done (52.5%). The incidence increases when they are younger, and it is more frequent with pathological findings in the bronchoscopy; the children with bacterial growth in BAL have fever more frequently than in the group that did
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Pedro-Botet found a 27% fever, and 0% post-bronchoscopy bacteremia without sedation, associated with liver disease, end-stage renal disease, and the presence of bronchial biopsy as risk factors. The use of deep sedation does not seem to modify the incidence of post-bronchoscopy fever, which is around 27%. This frequency is within the usual values of post-bronchoscopy fever in the adult population, in studies conducted without sedation and superficial sedation, so it would seem that depression of consciousness secondary to hypnotic drugs does not play a role in the development of fever or infectious complications.

A study that analyzed the appearance of fever, hospitalization, and use of health resources in 41 patients and 33 controls, with 50 patients with conscious sedation with alfentanil, found an incidence of fever of 41%; 7 patients attended an unscheduled visit, of which 1 was admitted for bronchopneumonia, 2 for pneumonia, and 1 for stroke that could not be confirmed, without finding any risk factor for the development of fever.

Other studies that evaluated post-bronchoscopy fever also found no predictive factors due to comorbidities (age, caries, smoking, lung disease, alcoholism) or the techniques performed (BAL, bronchial biopsy, lung biopsy). Some studies identified the extreme ages of life, and pathological findings in endoscopy as risk factors for the development of post-bronchoscopy fever, although it could not be demonstrated in others. It is possible that there are different mechanisms involved in the development of post-bronchoscopy fever. When bronchoalveolar lavage (BAL) is performed in intubated and ventilated patients, an increase in temperature is observed at 3 hours, particularly in patients with pneumonia. This occurs with both bronchoscopic BAL and non-bronchoscopic lavage. This change in temperature correlates with a fall in mean arterial pressure and oxygenation, and with endotoxin levels in the bronchoscopic BAL.

Deep sedation does not significantly affect the quality of bronchoscopic (BAS; 23.8% grade 5, 17.8% grade 4 of Murray criteria), or the presence of oropharyngeal microbiota (56.4%) in BAS, which is found in different studies, with a 36.6% growth of potentially pathogenic bacteria. So, does not seems that lung contamination with bacteria of the oropharynx may explain the fever or infection after bronchoscopy.

Hemmers et al. studied 41 children who underwent BAL, and found 17% of post-bronchoscopy fever, 2.4% of bacteremia, and 0% of infectious complications. Picard et al. randomized 2 groups of immunocompetent children, without fever, to receive dexamethasone (0.5 mg/kg) or saline, to prevent fever after BAL. The group with serum had an incidence of post-bronchoscopy fever of 68%, versus 9.6% of the dexamethasone group, which would favor an inflammatory mechanism for the development of fever.

It has been suggested that the increase in temperature was mediated by the release of cytokines by alveolar macrophages. However, some investigations do not support this theory. The effect of BAL on systemic pro-inflammatory cytokines was studied in 30 patients with non-small cell lung cancer (NSCLC), and compared with 15 healthy volunteers. The characteristics of BAL, auscultation, temperature, radiography, neutrophils, systemic cytokines (IL-1 beta, IL-6, TNF- alpha), and BAL at baseline, at 4 and at 24 hours was compared. 11 patients (33%) had fever, and had a significant increase in systemic cytokines (IL-6, TNF-alpha at 4 and 24 hours after BAL) with respect to patients who did not have a fever. In contrast, the BAL of the group of patients without fever, had higher values of TNF-alpha and IL-6 than the group that had fever, reason why the authors conclude that the levels of cytokines, alveolar macrophages and the characteristics of BAL have no relationship with systemic pro-inflammatory cytokines.

It has been considered whether a greater mucosal airway surface damage during bronchoscopy may favor bacteremia; however, in a study with 44 cases treated with argon-plasma by endoluminal tumor, no infectious complications were observed, and a single positive blood culture (2.3%). It has been postulated that post-bronchoscopy fever could be related to changes that occur in the intestinal mucosa triggered by the bronchoscopy itself. Rigid bronchoscopy may be more aggressive to the mucosa than flexible bronchoscopy. However, the information is contradictory in this sense; there is no conclusive evidence of bacteremia after rigid bronchoscopy in children and adolescents. Ansley et al. performed routine blood cultures in 25 children undergoing rigid bronchoscopy, with 0% fever, 0% bacteremia and 0% infectious complications.

In experiments in animal model, bacterial translocation from the intestine to mesenteric ganglia has been seen in 47% of a group of rats subjected to rigid bronchoscopy (a rigid bronchoscopy model that consists of intubating the rat trachea with an intravenous catheter), even with microorganisms possibly coming from the airway (the same Pseudomonas was isolated in BAL). This translocation of intestinal microorganisms to the bloodstream can trigger a systemic inflammatory response and acute lung injury in rats, although, apparently, bacterial translocation is less frequent in humans than in rats. The importance of bacterial translocation is discussed: although some authors postulate that it is a physiological requirement for the development of immunocompetent cells by the intestinal lymphatic system, there is evidence that supports the fact that bacterial translocation contributes to the development of systemic inflammatory response and multi-organ dysfunction.

However, the cause of bacterial translocation during rigid bronchoscopy in rats is unclear. It is believed that 3 mechanisms can participate: bacterial overgrowth, deterioration of the defensive capacity of the host, and an increase in the permeability of the intestinal barrier. Although it could be multifactorial, we know that the intestinal mucosa is very sensitive to hypoxia and acidosis, and even brief periods of hypoperfusion can lead to increased permeability of the intestinal mucosa, which could allow the passage of bacteria or endotoxins to the systemic circulation. During rigid bronchoscopy, hypercapnia, hypoxemia and acidosis can occur, causing changes in the intestinal microcirculation, which can lead to bacterial translocation.

It has been postulated that bacterial translocation may be one of the mechanisms involved in the development of post-bronchoscopy fever. From this perspective, Nayci et al. evaluated the intestinal mesenteric flow in 47 adult patients undergoing flexible bronchoscopy. They showed a 39% decrease in mesenteric arterial flow measured by Doppler ultrasound, which persisted up to 4 hours after the bronchoscopy, which was accompanied by a 22% drop in basal oxygen levels, in addition to markers of ischemia-reperfusion injury. 19% had fever and 6.4% had positive blood cultures for Gram-negative bacilli, suggesting that it could be mediated by mesenteric ischemia and bacterial translocation.
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Atelectasis may be another cause of post-endoscopic fever. In a study evaluating patients undergoing submucosal resection in digestive endoscopy with deep sedation with propofol, it was observed radiologically that 19.5% of patients developed atelectasis, which, although the majority resolved spontaneously, 13% had fever and 8.8% had pulmonary infiltration.80 Drug-related fever has also been described, which in some cases can begin quickly after the administration of propofol or fentanyl.81 Anticholinergics have been described as responsible for pyrexia in children undergoing sedation with ketamine.82

Therefore, there are multiple possible causes of post-bronchoscopy fever, and it is not clear that the infection is the cause. The incidence of post-bronchoscopy fever and, most importantly, of post-bronchoscopy infections84 and of medical resources due to infectious complications,85 is similar when performing bronchoscopy with or without deep sedation. When we perform bronchoscopy with deep sedation, often we can see secretions going down by the posterior wall of the trachea. Until few years ago, we had the concept that the lung is sterile, without microorganisms in it, and that BAS may be contaminated with the oropharynx bacteria.

Bartlett72 recommends not systematically culture BAS since 98% of the BAS sample is lidocaine, which has an inhibitory effect on bacterial growth. On the contrary, several works (especially in the pediatric population) analyzed the detection of pathogens in the oropharynx or nasopharynx compared with BAL, finding a high negative predictive value of the nasopharyngeal aspirate, and high positive cultures (97% for pneumococcus, 89% for Mycoplasma pneumoniae) in children with pneumonia.84 In children with various lung diseases, cultures of the oropharynx have a sensitivity to detect the same bacteria in the BAL of 89%, with a specificity of 94% and a positive predictive value of 91%.85 It was investigated the ability of the oropharyngeal culture to predict the presence in the BAL of Pseudomonas and Haemophilus in children under 5 years with cystic fibrosis, finding that the absence of them has a high negative predictive value, but that their isolation in the oropharynx has a positive predictive value of 44%.86

Other studies find similar concordances in children with cystic fibrosis, with a positive predictive value of 41%88. In fact, the use of cultures of the oropharynx to guide antibiotic therapy in children with cystic fibrosis is the usual practice in some centers.89 In adults, it was compared by PCR (Film Array Respiratory Panel, which investigates 17 viruses and 3 bacteria causing respiratory infection) the microbiological results in a nasal sample and in a BAL sample, finding a 77% agreement between both samples (23% it has the same pathogen and 77% shows absence of pathogens).88 In the 23% discrepancy, the BAL has greater profitability than the nasal swab.89

The presence of potentially pathogenic bacteria in pharyngeal exudate of adult patients with stable phase bronchiectasis is 18%, and 100% of bacteria considered nonpathogenic.90 The diagnostic value of the growth of potentially pathogenic bacteria in bronchoscopic specimens will depend on the clinical context. Angrill et al.91 identified 64% of bronchial colonization in patients with stable phase bronchiectasis (mainly Haemophilus influenzae (55%) and Pseudomonas sp. (26%) and Pneumococcus (12%), with 30% resistance to antibiotics, concluding that sputum culture is an alternative to BAL and the protected brush in these patients.91

Patients with lung cancer can have a 30% colonization of their lower airway, with a predominance of pneumococcus and staphylococcus.90 In turn, the airway of patients without respiratory pathology can be colonized by potentially pathogenic bacteria.91 Weinreich et al.91 found a 10% colonization in the BAS (bronchial lavage) of patients without chronic respiratory pathology who underwent bronchoscopy for a pulmonary nodule or hemoptysis, compared with 43% colonization in COPD and 63% in patients with bronchiectasis,91 which may call into question the behavior of not routinely cultivating BAS. In fact, Dickson et al.29 analyze, using molecular techniques, the origin of the lung microbiota of healthy people (by BAL and 7 brushed with different protected catheter: brushing the working channel of the bronchoscope, brushing the proximal, middle tracheal wall, and distal in carina, brushed in proximal intermediate bronchus, distal intermediate bronchus, and entrance of the middle lobe bronchus, and by bilateral BAL), and conclude that the pulmonary microbiome comes from the oropharyngeal microbiota, and that the main mechanism is due to microaspiration of oropharyngeal content, rather than contamination of the bronchoscope when passing through the oropharynx, or by contiguous dispersion through the bronchial mucosa, which have a minimal participation.95

Thus, the lung of healthy people, not only is not sterile, but the mechanism of arrival of the bacteria would be by subclinical microaspirations, which questions the argument of BAS contamination due to the passage of the bronchoscope through the oropharynx.92 In fact, these authors conclude that bronchoscopy is useful for investigating the pulmonary microbiome.92

Similarly, Bassis et al.,93 investigated the microbiome of the nasal cavity (swab), oropharyngeal (lavage), pulmonary (BAL) and gastric (gastric aspirate) in 28 healthy people. They find that the stomach and mouth are the ones with the greatest load and bacterial richness. They show that BAL is not contaminated with the passage of BCF through the oropharynx. The mouth and lung microbiota are very similar, although to a lesser extent at the pulmonary level. The nose and lung microbiota are not similar. This suggests that, not only we have microorganisms in the lung, but the microbiota of the lung comes from the migration of microorganisms from the mouth and oropharynx, through microaspirations.93

The pulmonary microbiome has been investigated in different respiratory diseases.94–102 Smoking patients without spirometric alterations seem to have a microbiota similar to non-smokers and mild COPD, while patients with moderate and severe COPD show a lower diversity of bacteria, which include Pseudomonas, Streptococcus, Prevotella, Fusobacterium, Haemophilus, Veillonella, and Porphyromonas.101 Severe COPD show an impoverished microbiome in terms of species diversity, with a predominance of potentially pathogenic bacteria, with loss of the resident microbiota, and development, in particular, of the genera Proteobacteria (44%), Firmicutes (16%), and Actinobacter (13%).100 Severe COPD patients, colonized by Pseudomonas, show a similar microbiome during exacerbations, than those previously not colonized, although with metabolic functional changes.98,102 The microbiome of severe asthmatic patients has been studied, under corticoid treatment, showing abundant presence of Bacteroides, Firmicutes, Proteobacteria, Actinobacteria, Streptococcus and Prevotella, Legionella and Fusobacteria, were present in a smaller amount.100 However, there were genomic differences between the results obtained in bronchial biopsies and BAS.100

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Therefore, traditional BAS culture techniques have low sensitivity and are not sufficient to demonstrate the diversity of the pulmonary microbiome. However, BAS and BAL have proven useful for the detection of DNA fragments that allow the evaluation of the pulmonary microbiota, in health and in different pathologies. So, our lungs not only are not sterile, but bronchoscopy is useful for the study of microbiota of the lung, and this, probably is independent if we use or do not use deep sedation for patient comfort.

**Conclusion**

Infectious complications after bronchoscopy are rare. The depression of consciousness secondary to deep sedation used in bronchoscopy does not favor the development of fever or infectious complications. Approximately, 1/4 of the patients develop fever. The mechanisms for the development of post-bronchoscopy fever are not clear, but the evidence does not suggest that it is of infectious origin. We have evidence that fever after bronchoscopy may have an inflammatory etiology. With the evidence we have, the use of prophylactic antibiotics does not seem to be justified at present.

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**Conflict of interest**

Author has declared there is no conflict of interest.

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