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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

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Abbreviations: FB, flexible bronchoscopy; TBNA, transbronchial needle aspiration; BAS, bronchoaspirate; BAL, bronchoalveolar lavage; ATB, antibiotics; EBUS, endobronchial ultrasound; NSCLC, non-small cell lung cancer

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) is associated with fever more frequently than other techniques).[19,22,23] However, in the adult population, this data usually refer to bronchoscopy performed without sedation, so it is possible that using sedation, and in particular, deep sedation, the rate of post-bronchoscopy fever is higher. In fact, it has been proposed to reduce the contamination of bronchoscopic samples by microorganisms of the oropharynx by using nebulized lidocaine instead of liquid, and passing the bronchoscope through an orotracheal tube.[24]

Although fever after a bronchoscopy can occur in 1/4 of the patients, infectious post-bronchoscopy complications are rare. In 1975, the first case of bacteremia and death secondary to bronchoscopy were described in a patient with respiratory infection who later died due to bacteremia.[25] There are reports in the literature of post-bronchoscopy infectious complications, such as pneumonia and pneumococcal sepsis,[26,27] sepsis due to Gram-negative bacillus,[25] pneumococcal meningitis,[28] post-transbronchial needle aspiration (TBNA) purulent pericarditis,[29,30] 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.,[29] 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 13/132 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.[22,34–36] Dürschmied describes 2.9% transient bacteremia post-bronchoscopy with biopsies.[37]

Yigla et al.,[38] 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.[23] 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

not have LAB with bacteria. None of the children had bacteremia. The characteristics of BAL were similar in terms of cellularity, IL-8, and alveolar macrophages.[23] The bacteremia associated with the use of a telescoped catheter was investigated in patients in intensive care with pneumonia, with 11% positive blood cultures, which were considered contamination, and concluding that bacteremia is very rare, even in this population.[39]

Witte et al.,[40] systematically performed culture of blood of 47 a febrile patients during 50 TBNA, at 5 and 30 minutes, and then if they had a fever in the first 24 hours. 10% of the patients had fever, with blood cultures that were all negative, and concluded that TBNA is a procedure with a low risk of bacteremia, and that, therefore, it does not require prophylaxis of endocarditis.[40] The studies that investigated the usefulness of giving prophylactic antibiotics did not find differences.[41] Prophylactic azithromycin has been used to prevent infectious complications of bronchoscopy with biopsy[41]. Kanazawa et al. randomized 930 patients to receive azithromycin 500mg for 3 days after bronchoscopy, cefcapene 300mg/day for 3 days, and compared it with a control group. The incidence of respiratory infection of the whole series was 1.61%; in the group without antibiotics it was 2.9%, while in the azithromycin group it was 0.7%, without reaching statistical significance. If only patients with pathological bronchoscopy were considered, post-bronchoscopy respiratory infection was 14.8% in the control group, 7.1% in the cefcapene group, and 3.0% in the azithromycin group. All patients who developed pneumonia had bronchogenic carcinoma. The microorganisms found were *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* in the control group, with *Acinetobacter* sp. listing in both groups with ATB. The groups with ATB had neither *Staphylococcus aureus* nor *Streptococcus pneumoniae*.[41] The only risk factor identified in this study was having bronchogenic carcinoma,[41] although other studies had identified age, distance from the nodule to carina, and the diameter of the lesion as risk factors for developing post-biopsy respiratory infection.[42,43]

Antibiotic prophylaxis is not recommended for bronchoscopy according to the 2015 edition of the ESC Guidelines for the management of infective endocarditis of the European Society of Cardiology because there is no compelling evidence that bacteraemia resulting from endscopic procedures causes infectious endoscarditis. From the 2008 American Heart Association guideline, prophylactic antibiotics are no longer recommended for diagnostic bronchoscopy. For invasive endoscopic procedures in high-risk patients (prothesic valves or material, prior endocarditis) and active infection, the recommendations are not clear or straight forward.

Kanemoto found an incidence of post-bronchoscopy fever of 6.7% and of pneumonia of 5.6%, although the incidence in people older than 70 years was lower (3.6% and 4.2%).[41] Wainwright identified the presence of previous bronchitis, or the growth of pneumococcus and Pseudomonas as predictors of post-BAL fever in children under 6 years of age with cystic fibrosis, which occurred in 21% (8.7% had a fever >38.5°C), and 12.3% lower than 38.5°C).[44] In the Wainwright study,[44] unlike the Kanazawa study,[41] the use of ATB was not associated with fewer episodes of fever.

The fever has also been described in ultrasound bronchoscopy (EBUS) which appears in approximately 20%, with a very low incidence of infectious complications (1 pneumonia and 2 mediastinal abscesses in 684 procedures).[45] Steinfort et al.,[46] found 7% of post-EBUS bacteremia, with microorganisms of the oropharynx, and 35% of cultures positive for the washing liquid of the puncture needle.[46]

It is important to discern whether, in addition to the endoscopic procedure itself, there may be a risk of infection secondary to the drugs used in sedation. It has been postulated that propofol could favor bacterial infections, by modulating the immune response of the host.[47] In cell cultures, propofol was associated with a decrease in pro-inflammatory molecules of immune response signaling (decreased TNF-alpha and inducible nitric oxide synthetase), suppression of prostaglandin E2 production by macrophages and dendritic cells[48] (which decreases the production of inflammatory cytokines), as well as a decrease in the phagocytic activity of macrophages.[49–51] In a study with rats inoculated with *Listeria monocytogenes*, it was observed that when sedated with propofol, the bacterial load increased approximately 10,000 times in the target organs, compared with the animals of the control group. This increased susceptibility persisted for several days (up to 96 hours) once the effect of sedation disappeared. On the contrary, rats subjected to sedation with pentobarbital (which also acts by GAB Aergic mechanism), or with ketamine (which acts by an alternative mechanism to the GABA system), did not show this greater susceptibility to systemic infection by Listeria. In this study, propofol altered the expression of cytokines and chemokines during Listeria infection, making Listeria clearance difficult by inhibiting the recruitment and / or activity of immune cells at sites of infection.

It was observed that propofol produced a decrease in the macrophages of the splenic marginal zone, with the consequent spread of infection by Listeria.[47] These effects do not only occur for the defensive capacity of the host against Listeria, but also against methicillin-resistant *Staphylococcus aureus*.[47] Although the hypnotic effect of propofol is brief (5 minutes), the prolonged effects on the immune response can be explained by its pharmacodynamics. Propofol is a very lipophilic drug, which once within the bloodstream is rapidly distributed in tissues, and in particular, in fatty tissues. At the liver level, it is modified by cytochrome P450-2A6, and its metabolites pass into the blood and persist for several days in the tissues,[52] which, it has been speculated that it could be the mechanism by which, the immunological effect of propofol, it persists up to 4 days.[47] In a study with rats to which, as a septic model, the bowel was ligated and then punctured, it was observed that the continued use of propofol for more than 24 hours, increased the mortality of the sedated rats with propofol, compared with the rats exposed to anesthetic gases.[53]

However, these immunological alterations caused by propofol are not evident in the absence of infection, so it is possible that propofol can interact at the level of the signaling cascade triggered by bacterial invasion.[47] The incidence of post-bronchoscopy pneumonia reaches 1% in some studies in which bronchoscopy is performed with deep sedation.[54] Takaguchi et al.,[55] developed a predictive score for the development of post-bronchoscopy pneumonia in a retrospective study of 237 patients with lung cancer (incidence of pneumonia 6.3%) and validated it prospectively in a sample of 241 patients (incidence 4.1%), identifying the age over 69 years, active smoking, and central location of the tumor as risk factors for developing post-bronchoscopy pneumonia. They developed a score in which they give 1 point to each item, with an incidence of pneumonia of 0, 2.9 and 9.7%, with scores of 0, 1 and 2 respectively.[55]

Although bacterial infections are very uncommon, post-bronchoscopy fever, both in flexible bronchoscopy and ultrasound bronchoscopy, is more frequent, with incidences ranging from 0 to 68 %.[5,19,22,23,34,36–42,44–46,55–69]

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Pedro-Botet found a 27% fever, and 0% post-bronchoscopy bacteremia without sedation, associated with liver disease, endobronchial lesion, and the practice of bronchial biopsy as risk factors.[34] The use of deep sedation does not seem to modify the incidence of post-bronchoscopy fever, which is around 27%.[54] 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 bronchospasm, 2 for pneumonia, and 1 for stroke that could not be confirmed, without finding any risk factor for the development of fever.[70]

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).[58] Some studies identified the extreme ages of life, and pathological findings in endoscopy as risk factors for the development of post-bronchoscopy fever,[22,23] although it could not be demonstrated in others.[42,62] It is possible that there are different mechanisms involved in the development of post-bronchoscopy fever**.**[71] 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**.**[71]

Deep sedation does not significantly affect the quality of bronchoaspirate (BAS)(23.8% grade 5, 17.8% grade 4 of Murray criteria), or the presence of oropharyngeal microbiota (56.4%) in BAS,[54] which is found in different studies,[72,73] with a 36.6% growth of potentially pathogenic bacteria**.**[54] So, does not seems that lung contamination with bacteria of the oropharynx may explain the fever or infection after bronchoscopy.[54]

Hemmers et al.,[68] studied 41 children who underwent BAL, and found 17% of post-bronchoscopy fever, 2.4% of bacteremia, and 0% of infectious complications.[68] Picard et al.,[63] 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.[74] 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-1beta, IL-6, TNF-alpha), cytokines in 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.[74]

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%).[57] 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.[61] Ansley et al.,[61] performed routine blood cultures in 25 children undergoing rigid bronchoscopy, with 0% fever, 0% bacteremia and 0% infectious complications.[61]

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),[75] 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,[76] although, apparently, bacterial translocation is less frequent in humans than in rats.[77] 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.[77]

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.[77] 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.[75,78]

It has been postulated that bacterial translocation may be one of the mechanisms involved in the development of post-bronchoscopy fever.[75] From this perspective, Nayci et al.,[79] 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.[79]

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 infections[54] and of medical resources due to infectious complications[83], 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.

Bartlett[72] 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.[87] In adults, it was compared by PCR (Film Array Respiratory Panel, which investigates by PCR 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.[88]

The presence of potentially pathogenic bacteria in pharyngeal exudate of adult patients with stable phase bronchiectasis is 18%, and 100% of bacteria considered nonpathogenic.[89] The diagnostic value of the growth of potentially pathogenic bacteria in bronchoscopic specimens will depend on the clinical context. Angrill et al.,[89] identified 64% of bronchial colonization in patients with stable phase bronchiectasis (mainly *Haemophilus influenzae* (55%) and *Pseudomona* 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.[89]

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.,[92] 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.[92]

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.[95,102] The microbiome of severe asthmatic patients has been studied, under corticoid treatment, showing abundant presence of *Bacteroids*, *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.[94,99] 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.[94,99] 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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