Airways colonizations in patients undergoing lung cancer surgery

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Summary

Lung cancer remains the main leading cancer-related cause of death in the world. For early-stage tumor, surgery stands out as the best curative option offering the greatest chance for cure. Despite improvement of per- and postoperative management, surgery continues to carry a high morbidity with a significant mortality. Among postoperative complications, respiratory failures (nosocomial pneumonia and acute respiratory distress syndrome) are currently the most frequent and serious, as well as being the primary cause of hospital death, after a lung resection for cancer. Because infectious etiologies have been highly incriminated in the development of these pulmonary complications, microbial airways colonizations (AWCs) are supposed to be an essential first step in the pathogenesis of these failures occurring in hospitalized and chronically ill individuals. These patients fulfill all the predisposing factors to bronchial colonizations and are particularly exposed to the development of respiratory failures in the postoperative setting, when secretion clearance and cough reflex are impaired. Under immunosuppressive conditions, AWC should act in a manner that increases its ability to stimulate microorganisms and increase the risks of superimposed infections. Few studies have addressed the problem of AWCs in patients submitted for lung cancer surgery. Because of several limitations, especially the lack of exhaustive microbiological studies, the conclusions that can be reached remain inconclusive. This review aims to report the existing literature on this critical and controversial issue, focusing on their specific incidence, their predisposing factors, their correlation with development of respiratory failures, and, in turn, the reliability of the current antibiotic prophylaxis for their prevention.

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Keywords: Lung cancer; Airways; Microbial colonizations; Bronchoscopy; Nosocomial pneumonia; ARDS

1. Introduction

Lung cancer is the main leading cancer-related cause of death worldwide in both genders [1–3]. To date, current curative strategies are based mainly on surgery, which offers the greatest chances of cure for patients with an early-stage disease. With the advances made in anesthesia and surgery, the number of patients submitted to surgery is expected to increase continuously, including in marginally operable candidates.

Despite improvements in per- and postoperative care, surgery continues to carry out a high morbidity and a substantial mortality. Surgery-related mortality ranges between 0% and 4% after segmentectomy, between 0% and 10% after lobectomy and between 3% and 21% after pneumonectomy [4–8]. Among postoperative complications, respiratory failures remain the most frequent and serious, being the primary cause of in-hospital death in 22–75% of the cases [4]. These facts have stimulated continuous efforts in the prevention, diagnosis, and treatment of postoperative pulmonary complications.

Postoperative respiratory complications are a heterogeneous group of diseases with various causes and pathogenic mechanisms. Reasons for this pulmonary morbidity are multifaceted, and those due specifically to surgery are probably very difficult to segregate from those due to perioperative anesthetic management, to postoperative events, and to the patient himself. However, there is growing evidence that these different forms of respiratory failures should have a common substratum, notoriously infectious, with similar clinical presentations [4,5,9]. The clinical frame includes tracheobronchitis, pneumonia, and acute respiratory distress syndrome (ARDS). Pneumonia is considered as the main concern of a dramatic continuum leading to ARDS and represents nearly one-third of all care-related infections. The incidence of pneumonia after a lung surgery has been addressed in a meta-analysis [10]. Postoperative pneumonia remains the most frequent complication after lung resection, occurring in 10% after lobectomy and between 3% and 21% after pneumonectomy [4–8].
resection is estimated between 2% and 20% with a related mortality between 15% and 75% [4]. The incidence of these respiratory failures has varied poorly since the last decade and their severity remains invariably stable over time. A vast majority of these respiratory failures are mostly bacterial but a part of them is frequently undetermined with inconclusive postoperative microbiological results [6,10].

Because infectious etiologies have been highly incriminated in the occurrence of these respiratory failures, airways colonizations (AWCs) are supposed to be an essential first step in the pathogenesis of nosocomial pneumonia and ARDS occurring in hospitalized and chronically ill individuals fulfilling all predisposing factors to bronchial colonization [10–14]. Bronchial colonization would be the result of an equilibrium in which the host’s defenses succeed in limiting, but not eradicating, the microorganisms adhering to the bronchial epithelium. Lung infection would be the result of a lowering of the host’s cellular and humoral defenses at a specific time, or of the presence of an inoculum in a sufficient quantity or of a sufficient virulence to produce it [14–19]. AWC is supposed to facilitate the development of pneumonia in the postoperative setting, when secretion clearance and cough reflex are impaired. Under immunosuppressive conditions, such as surgery, colonizations of the respiratory mucosal surface act in a manner that increases its ability to bind microorganisms and increase the risks of superimposed infections.

Few studies have addressed the problem of AWCs in patients submitted to lung cancer surgery [10–14]. Because of several limitations, conclusions that can be reached remain inconclusive. This review aims to report the existing literature on this critical and controversial issue, focusing on their specific incidence, their predisposing factors, their correlation with development of respiratory failures, and, in turn, the reliability of the current antibiotic prophylaxis for their prevention.

2. Materials and methods

English-language reports of published studies on AWC in lung cancer surgery were reviewed by cross-referencing the following medical subject headings (MeSH) keywords and text words: airways colonizations, lung cancer, respiratory complications, nosocomial pneumonia, thoracic surgery, ARDS, bronchoscopy, and antibioprophylaxis. Databases searched included PubMed, EMBASE, and Cochrane Database of Systematic Reviews. Bibliographies of original articles were manually reviewed for additional articles. Non-English language reports were also identified in PubMed, using the same keywords, to supplement our search.

We conducted a meta-analysis, which evaluates the published literature in a qualitative and quantitative way by comparing and integrating the results of different studies. The main goal of the meta-analysis was to assess the correlation between preoperative AWC and occurrence of postoperative respiratory complications. Studies included in the meta-analysis had to assess AWC in patients submitted for lung surgery, and had to provide related numbers of respiratory complications in both colonized and non-colonized groups. Meta-analysis was carried out using odds ratio (OR) and confidence interval (CI) 95%. The OR represents the odds of a positive association between AWC and postoperative respiratory complications in the colonized group in comparison to the non-colonized group. An OR of up to 1 if the 95% CI does not include the value 1 or 0 was considered as statistically significant at the \( p < 0.05 \) level. In our study, both fixed and random effect models were employed. The fixed effect model is based on the assumption that the AWC in each study is constant, whereas the random effect model is based on the assumption that there is variation between studies. Thus, the ratios calculated in the random effect model are more conservative than those calculated in the fixed effect model. In a meta-analysis of surgical research, the random effect model is preferable due to a number of sources of heterogeneity, including various risk profiles, selection criteria for each surgical technique, study design, study start date, and duration of follow-up. Heterogeneity between studies was investigated by the standard chi-squared Q-test. Analysis was performed by Statistical Package for Social Sciences (SPSS) version 13.0 for Windows (SPSS Inc., Chicago, IL, USA), Microsoft Excel 2002 (Microsoft Corporation, USA), and Medcalc 11.3 (MedCalc Software, Mariakerke, Belgium).

3. Incidence of AWCs

Colonization is classically defined by isolation of microorganisms into airways with positive cultures in asymptomatic patients. Patients are considered to have colonization whenever a microorganism is isolated above specific thresholds: \( \geq 10^2 \) cfu (colony-forming unit) ml\(^{-1}\), when investigated by protected specimen brush (PSB) or \( \geq 10^4 \) cfu ml\(^{-1}\) for bronchial aspirates [11,12].

To provide an evidence-based statement on their clinical relevance in the setting of lung cancer surgery, it is obviously necessary to describe the incidence of these colonizations in different clinical situations.

3.1. In healthy non-smoker patients

Healthy non-smokers are generally considered as free from bacterial colonization of the lower airways [20,21]. Nevertheless, there is very little information dealing with this issue. Cabello et al. have found that only 1 of 10 healthy and asymptomatic subjects had a true respiratory pathogen isolated from the lower airways [11]. Using PSB and bronchoalveolar lavage (BAL) to study the distal airways of eight healthy individuals, Kirkpatrick and Bass have found that only one BAL specimen yielded one potential pathologic microorganism (PPM) [22]. These studies have underlined the efficacy of lung defenses in healthy non-smoker individuals in maintaining the near sterility of the lower airways.

3.2. In smokers and in chronic obstructive pulmonary disease patients

In healthy smokers, bacterial colonization is frequent, ranging between 29% and 33% [15,23]. Qvarfordt has demonstrated that 29% of asymptomatic smokers were colonized, and this was comparable to the fraction of...
colonized chronic obstructive pulmonary disease (COPD) patients [23–25]. In COPD patients, Monso has demonstrated that 25% of 40 stable COPD patients had colonization of the distal airways, mainly of *Haemophilus influenzae* and *Streptococcus pneumoniae* [25]. It has been speculated, particularly in COPD patients, that the persistence of microorganisms in distal airways could worsen the evolution of the chronic underlying disease [15,16,19]. Similar results were reported by Riise [24] studying 18 COPD patients where 12 have presented a documented colonization (66%). Cabello has reported a higher rate of colonization in COPD patients (83%). However, 76% of the colonizing agents were non-PPMs belonging to the oropharyngeal flora.

3.3. *In lung cancer patients*

Colonization patterns in patients with bronchogenic carcinoma do not differ from those found in COPD patients, indicating that both populations are very similar. Reporting on 33 patients, Cabello et al. have reported that 42% of their patients were colonized (36% of PPMs and 64% of non-PPMs) [11]. Liaw has shown that Gram-negative bacilli and anaerobes may be found in distal airways below the bronchial obstruction [26]. Hirakata has examined the bacterial colonization of the upper respiratory tract of 110 patients with primary lung cancer, 75 patients with non-malignant lung diseases, and 45 healthy volunteers [27]. The frequency of bacterial colonization of the upper respiratory tract was significantly higher in lung cancer patients (59.1%) than in non-malignant lung diseases patients (37.3%) and healthy volunteers (37.8%). The frequency of Gram-negative colonization was significantly higher in lung cancer patients than in other subjects.

3.4. *In lung cancer patients undergoing surgery*

A systematic review of the literature is presented in Table 1. This summarizes six prospective studies and one retrospective study.

In 1991, Wansbrough-Jones investigated 75 patients subjected to pulmonary or pleural resection by performing cultures from samples obtained by preoperative BAL [28]. He found pathogenic microorganisms in 23%, with *H. influenzae* found most frequently. Of the 75 patients, 11% developed infectious respiratory complications in the postoperative outcome. The likelihood of developing postoperative chest infection was 42% in those patients whose lavage culture was positive for bacterial pathogens compared with 4.8% for those whose culture was negative. In 2002, Sok designed a prospective study to verify the origin of the pathogens that cause pleuropulmonary infections after lung cancer resection [29]. He studied samples of sputum 3 days before, during, and 3 days after the operation. The infections appeared at 4.3 days. In 75% of cases, the microorganisms that caused the lung infections were Gram-negative bacilli and *Candida albicans*. These were isolated in 18%, 13%, and 63% of sputum samples, pre-, intra-, and postoperatively, respectively. He also found a strong association between the pathogens found in the sputum obtained 3 days after the operation and those found in the sputum of patients, who developed a lung infection. The author suggested that the colonization of the airway generally occurs during the postoperative period, from the patient’s oral cavity, pharynx, and hypopharynx.

In 2002, Ioanas investigated 41 patients with resectable cancer [13]. In his prospective observation based on PSB, he found that 41% presented a bacterial colonization, mainly by PPMs (36%). Body mass index (BMI) > 25 kg m⁻² and proximal location of the tumor were the sole two independent factors of AWC in the multivariate analysis. However, he did not find any correlation between AWC and postoperative infection in his univariate analysis. In the prospective evaluation by Belda in 2005, based on bilateral PSB before thoracotomy, AWC was present in 65 of 78 patients (83%) [12]. Microbiological agents included PPMs in 36% and non-PPMs in 72% of patients. He found a positive correlation between AWC and postoperative pulmonary complications on multivariate analysis. These results have been confirmed in 2006 by Schussler. In an observational and prospective study, he investigated 168 patients with resectable lung cancer [10]. Based on bilateral bronchoscopic aspirates, he demonstrated AWC in 22.8% of patients. The bacterial agents were mainly *H. influenzae*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>n</th>
<th>Samples</th>
<th>AWC rate</th>
<th>Postoperative documented microorganisms</th>
<th>Respiratory infections rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wansbrough-Jones [28]</td>
<td>P</td>
<td>54</td>
<td>BAL in resected specimen</td>
<td>12/54 (22%)</td>
<td>H. influenzae 8 (66%) S. pneumoniae 1 (8%) S. aureus 1 (8%)</td>
<td>8 (10, 7%)</td>
</tr>
<tr>
<td>Sok [29]</td>
<td>P</td>
<td>194</td>
<td>Sputum samples</td>
<td>23/126 (18%)</td>
<td>Gram-negative spp 23 (18%) H. influenzae 8 (35%) S. pneumoniae 3 (13%)</td>
<td>34/194 (18%) 5/12 (12%)</td>
</tr>
<tr>
<td>Ioanas [13]</td>
<td>P</td>
<td>41</td>
<td>PSB and samples in resected specimen</td>
<td>17/41 (41%)</td>
<td>Pseudomonas spp. 3 (13%) S. pneumoniae 3 (5%)</td>
<td>24/78 (31%)</td>
</tr>
<tr>
<td>Belda [12]</td>
<td>P</td>
<td>78</td>
<td>Bronchoscopic aspirate and PSB</td>
<td>65/78 (83%)</td>
<td>H. influenzae 2 (3%) S. pneumoniae 9 (29%) Polymicrobial 9 (29%)</td>
<td>42/168 (25%)</td>
</tr>
<tr>
<td>Schussler [10]</td>
<td>P</td>
<td>168</td>
<td>Bronchoscopic aspirate</td>
<td>31/136 (22.8%)</td>
<td>H. influenzae 19 (61%) S. pneumoniae 9 (29%) Polymicrobial 9 (29%)</td>
<td>87/246 (34%)</td>
</tr>
<tr>
<td>Dancewicz [30]</td>
<td>P</td>
<td>44</td>
<td>Bronchoscopic BAL</td>
<td>26/44 (59%)</td>
<td>H. influenzae 7 (26%) S. aureus 4 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Yamada [31]</td>
<td>R</td>
<td>626</td>
<td>Sputum samples</td>
<td>Non COPD: 50/475 (10.5%) COPD: 30/151 (20%)</td>
<td>H. influenzae 21 (3.4%) S. pneumoniae 19 (3%) S. aureus 13 (2.1%)</td>
<td>40/626 (6.4%) Non COPD: 17/475 (36%) COPD: 23/151 (14%)</td>
</tr>
</tbody>
</table>
(61%), *S. pneumoniae* (29%), and polymicrobial (29%). He also confirmed a positive correlation between AWC and postoperative pulmonary complications on multivariate analysis.

Recently, Dancewicz has reported AWC in 59% of his 44 patients [30]. However, none of their patients developed postoperative pulmonary infections. In 2009, Yamada reported the results of a retrospective evaluation of 626 patients where all the patients had pre- and postoperative sputum samples or aspirates [31]. AWC was present to the extent of 10.5% in non-COPD patients and 20% in COPD patients. Again, the authors found, on multivariate analysis, a positive association between AWC and postoperative pulmonary complications.

### 4. Association between AWC and postoperative pulmonary complications

Despite a huge variability in its incidence (10.5–83%), there is an indisputable presence of colonizing agents of the lower respiratory tract in patients undergoing lung cancer surgery [10–14,28–30]. However, correlations between these findings and their clinical impacts remain controversial.

Table 2 and Fig. 1 present the results of our meta-analysis including seven selected studies and including 1083 patients. Of them, 291 were considered as colonized patients (26%) and the remaining 792 patients constituted the non-colonized group (74%). Postoperative respiratory complications occurred in a total of 149 patients (13%): 66 (23%) patients in the colonized group and 83 (10.4%) in the non-colonized group. Five of the seven studies summarized in Tables 1 and 2 find a positive correlation between AWC and postoperative pulmonary complications [12,10,28,29,31]. Three of these five studies demonstrate a strong correlation where AWC appeared as an independent factor on multivariate analysis [10,12,31]. Only two studies find a lack of correlation between AWCs and postoperative respiratory failures [13,30]. Results of our meta-analysis indicated an OD of 2.3 (1.58–3.48 95% CI) in the fixed model and 2.44 (1.45–

<table>
<thead>
<tr>
<th>Study</th>
<th>Postoperative respiratory complications in colonized group</th>
<th>Postoperative respiratory complications in non-colonized group</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wansbrough-Jones [28]</td>
<td>5/12</td>
<td>2/42</td>
<td>14.286</td>
<td>2.3–88.69</td>
</tr>
<tr>
<td>Sok [29]</td>
<td>20/99</td>
<td>14/95</td>
<td>1.465</td>
<td>0.62–3.10</td>
</tr>
<tr>
<td>Ioanas [13]</td>
<td>2/17</td>
<td>3/24</td>
<td>0.933</td>
<td>0.13–6.29</td>
</tr>
<tr>
<td>Dancewicz [30]</td>
<td>0/26</td>
<td>0/18</td>
<td>0.698</td>
<td>0.01–36.79</td>
</tr>
<tr>
<td>Yamada [31]</td>
<td>9/78</td>
<td>31/458</td>
<td>1.797</td>
<td>0.82–3.93</td>
</tr>
<tr>
<td>Total (fixed effects)</td>
<td>66/291</td>
<td>83/792</td>
<td>2.330</td>
<td>1.58–3.42</td>
</tr>
<tr>
<td>Total (random effects)</td>
<td>66/291</td>
<td>83/792</td>
<td>2.447</td>
<td>1.45–4.11</td>
</tr>
</tbody>
</table>
4.11 95% CI) in the random model. To conclude, based on the existing information summarized in our meta-analysis, there is reasonable evidence documenting a correlation between preoperative AWC and postoperative respiratory failures.

If a statistical correlation between AWC and postoperative complications is likely evident on different multivariate analysis [10,12,31], it is not the case from a microbiological viewpoint. Correlation between microbiological agents found pre- and postoperatively is not clear. Ioanas have pointed out the problem, finding only two positive cultures of the seven patients developing postoperative pulmonary complications. These two cultures did not correspond to those isolated preoperatively in bilateral PSB [13]. This problem was also reported by Sok, which demonstrated that preoperative positive cultures were mainly of Gram-positive (77%) or Gram-negative bacteria (20%), whereas postoperative positive cultures were mainly of Gram-negative (55%) and Gram-positive bacteria (37%) [29]. By contrast, some authors have demonstrated an association between pre- and postoperative cultures [10,28]. Wansbrough-Jones found that seven patients developed postoperative pneumonia with the same agents identified preoperatively [28]. In Schussler’s series, among the nine colonized patients, who developed documented postoperative pneumonia, a concordance between the bacteria responsible for colonization and postoperative pneumonia could be proven in six cases (85%) [10]. Belda also found a correlation between AWC and postoperative pneumonia [12]. Comparing the PPMs isolated during the peroperative examination and those isolated at the onset of infection, total concordance of PPMs was obtained in 21%, partial concordance was obtained in 21%, and no concordance occurred in 58%.

On the basis of these results, it is reasonable to consider that the relationship between peroperative colonization and postoperative infections is controversial and relatively weak, showing partial or total coincidence in only 42% cases of infection [12]. Moreover, patients without peroperative colonization by PPM are still at risk for postoperative respiratory infection. This moderate microbiological correlation, contrasting with the clinical evidence supported by prospective evaluation including multivariate analysis, emphasizes the imperfections of the current microbial sampling methods and the limitations of the traditional microbial cultures used [32]. Furthermore, it supports the current concept of multifaceted origins of respiratory failures where additional ‘hits’ participate to cause respiratory failures. Indeed, other mechanisms may be involved in the onset of postoperative respiratory failures and, especially, the postoperative inflammatory response. This has been suggested for postoperative pulmonary complications in esophageal cancer patients submitted to surgery [33].

5. Microbiological agents

5.1. Colonizing agents

What remains unclear is why postoperative documented pathogens are frequently different from those isolated in the preoperative period. From our literature review (Table 1), most series have reported *H. influenzae*, *S. pneumoniae* and *Staphylococcus aureus* as the most commonly identified colonizing agents into the airways of lung cancer patients [10,12,13,28–31]. Recently, Yamada et al. reported the distribution of preoperatively isolated PPMs into the airways of 626 patients submitted to lung cancer surgery. They divided colonizing agents according to PPMs related to community acquired pneumonia (CAP) (*H. influenzae* (3.5%), *S. pneumoniae* (3%), *Moraxella catarrhalis* (2%) and PPMs related to nosocomial pneumonia (NP) (*S. aureus* (2%), *Pseudomonas aeruginosa* (1%) and non-fermenting Gram-negative bacteria (1.8%) [31]. They confirmed that PPMs-CAP represented the main preoperative colonizing agents but they also emphasized that PPMs-NP were the main causative pathogens in the occurrence of respiratory failures.

5.2. Agents identified in postoperative outcome

The postoperative documentation of pathogenic agents is problematic. Between 29% and 50% of postoperative pulmonary infections remain not documented [10,12]. If documentation has been achieved, pathogenic bacteria are in most instances those classically reported for early hospital-acquired pneumonia [10,12,13,28–31]: *H. influenzae* (3—66%), *S. pneumoniae* (3—29%), and *S. aureus* (8—19%).

A polymicrobial etiology is recognized between 15% and 33% of patients. *Enterobacter* and *Pseudomonas* species are responsible for less than 10% of cases. In previous studies performed so far to assess microbiological characteristics of postoperative pulmonary infections, the results were somewhat similar. A team from Mayo Clinic [6] found that *Streptococcus* species and *H. influenzae* were responsible for 50% of all postoperative pulmonary complications, whereas Gram-negative pathogens (other than *Haemophilus* species) accounted for 31% of pneumonias. In the experience of Sok, [29] Gram-negative pathogens (other than *Haemophilus* species) were responsible for 71% of postoperative pulmonary complications and *Streptococcus* species were found in only 10% of cases. In the Schussler experience, a culture of intraoperative bronchial aspiration showed classical cultures: *H. influenzae* (41.7%), *S. pneumoniae* (25%), and other streptococci (12.5%) [10]. He also found that 22.2% of *S. pneumoniae* strains had a decreased sensitivity to penicillin G and 26% of *Haemophilus* strains were β-lactamase positive, these last figures being in agreement with available data on resistance in the setting of both community acquired respiratory infection and of medically treated lung cancer [34,35].

5.3. Unexpected agents

To our knowledge, previous reports have only focused their investigation on bacteriological cultures [10,12,13,28–31]. This constitutes a strong limitation because bacteria do not represent the sole microbial agents in a broad spectrum of potential pathogens. In fact, in the large microbial biodiversity, virus and fungi might also represent potential pathogenic microorganisms. Our group has reported the results of a prospective observational study based on preoperative bronchoscopic BAL in patients submitted for esophageal cancer surgery [36]. Our data suggested that preoperative AWC was relatively common (30%). Thirteen of the 45 BAL patients (28%) had a preoperative bronchial colonization by...
either PPMs (16%) or non-PPMs (13%). Among PPMs, cytomegalovirus (CMV) was cultured from BAL in four patients. One of the surprising results of our study was the 9% incidence of preoperative CMV detection in BAL group patients, and the 42% incidence of postoperative CMV infection, documented by open lung biopsy, in those patients who experienced ARDS postoperatively. CMV infection is a well-known problem in patients treated by high-dose chemotherapy for hematological diseases, in human-immunodeficiency virus (HIV)-infected patients, and in lung transplantation recipients [37]. Data on cancer patients are scarce, but CMV infection has been incriminated, particularly if steroids were a component of the therapy [38]. We have previously reported CMV as a possible cause of ventilator-associated pneumonia and ARDS [39]. Acquisition of the virus arises progressively from an early age, and, in developed countries, the overall seroprevalence is 30—70%. However, there is a huge variance in the incidence of CMV infection depending mainly on local ecology. Homosexual men, poor socioeconomic groups, and residents of developing countries have seroprevalence rates that can exceed 90% [37]. Other unexpected agents participating to AWC should be considered (Herpes simplex virus (HSV2), C. albicans, etc.) but data are unavailable.

6. Methods of microbiological analysis

Methods of assessment and microbiological analysis constitute two strong limitations in the investigation of AWC in lung cancer patients.

6.1. Methods of sampling

There is a general agreement that methods of microbiological assessment and identification of colonizing agents are not optimal. Studies summarized in Table 1 emphasize the variance between the different sampling methods used. For most studies, AWCs have been investigated by proximal samples such as sputum or tracheal aspiration [29,31], by bronchoscopic samples, [10,12,13,30] or by samples in the resected specimen [10,13,28]. As for diagnosis of ventilatory acquired pneumonia (VAP), most authors consider bronchoscopic sampling methods with quantitative cultures as the best reliable methods to determine optimal assessment of potential colonization [32]. This technique provides a good assessment of both proximal and distal airways. As a result, incidence of AWC when performed with endoscopy is increased compared with other traditional techniques. However, this method of assessment is exposed to potential contamination from oropharyngeal flora. By contrast, when cultures are obtained from distal airways, at best from lung parenchyma or from BAL performed in a lung-resected specimen, the incidence of AWC is lower, even negative [10]. This suggests that incidence of AWC is strongly dependent on the sampling methods used, second, that bronchial colonization should be limited to proximal airways.

6.2. Methods of cultures

Another limitation of the previous studies assessing AWC is related to the methods of microbiological identification. Knowledge of microorganisms in AWC and, more generally, in the environment has depended in the past mainly on studies of pure cultures in the laboratory. However, there are several limitations with culture methods. First, depending of the type of sample, isolation, and/or detection of potential microbial pathogens could be difficult in complex microbial samples contaminated by other bacteria or fungi. Second, culture methods are usually limited to a few selective or non-selective media for which many uncultured pathogens and anaerobes could be missed on these media and, thus, could not be detected. Recent data have demonstrated that 99% of organisms seen microscopically are not cultivated by routine techniques and required modern and innovating techniques to be identified [40,41]. It seems critical in this context to develop new media that could be more permissive for the isolation of new bacteria. Thus, development of new molecular techniques, such as 16S ribosomal RNA (rRNA) gene amplification and sequence directly from samples may be useful and will provide a new point of view of the problem. This has been successfully used for pleural infection [42] and in pneumonia [43]. Moreover, evaluation of the potential microbial diversity in these samples may be also assessed using molecular techniques including 16S rRNA gene clonal library sequencing or 16S rRNA gene pyrosequencing, as recently exemplified in the context of cystic fibrosis [44—46].

To date, there are no specific data on genetic and molecular assessment of AWC in patients submitted to lung cancer surgery. Finally, recent metagenomic studies of the human microbiome using high-throughput sequencing analysis are currently ongoing in many clinical microbiology areas including gut and skin surface [47—49]. Such a tool has been also recently used to characterize respiratory tract DNA viral communities in cystic fibrosis and non-cystic fibrosis patients [50].

7. Factors predisposing to AWC

There are numerous descriptions of risk factors for pneumonia that can coincide in the perioperative period and that would act by altering the balance between the host’s defense system and the causal microorganism in some way (alteration of the nutritional state, old age, deteriorated of predicted forced expiratory volume in 1 s (FEV1), chest pain, type of lung resection, etc.) (Fig. 2) [51—56]. AWCs could act as causal or an additive element but what constitute their predisposing risk factors remains unclear.

7.1. Smoking and COPD

The physical properties of cigarette smoke promote the deposition of particles in the lower airways, where they affect respiratory defense mechanisms at multiple levels [50]. In healthy smokers, bacterial colonization is frequent (33%) [15]. The pro-inflammatory effects of smoking overlap those induced by bacterial infection, especially neutrophilic infiltration of the airways. In ex-smokers, a persistent inflammatory process is seen in the central and small airways, which is indistinguishable from inflammation seen in current smokers [57—60]. Ongoing inflammation is present in BAL fluid and in bronchial biopsies among ex-smokers with COPD [61]. Therefore, to reliably distinguish the pro-inflammatory effects of
bacterial colonization from those related to active smoking requires limiting study to only ex-smokers.

For patient submitted to surgery, there is growing evidence that smoking cessation should be undergone weeks prior to surgery. In a prospective study, Barrera has provided evidence that smoking cessation in the weeks immediately prior to undergoing thoracotomy for the resection of lung cancer conferred a beneficial advantage decreasing the risks of pulmonary infections. Non-smokers had lower rates of all pulmonary complications and pneumonia than did all smokers [62]. However, the study was not designed to provide definitive conclusions in terms of microbiological AWC.

7.2. Intubation and oropharyngeal contamination

Patients submitted to lung cancer surgery are subjected to selective tracheobronchial intubation, mechanical ventilation, and, in many cases, bronchoscopy to check or reposition the tube used for the selective intubation. In a prospective trial including 194 patients, Sok supported the fact that the mechanism of airway contamination does not occur during anesthesia but rather in the early postoperative period secondary to silent aspiration, reflux, overspill, and manipulation in the intensive care unit (ICU) [29]. There were similar strains and a similar distribution of pathogens found in the postoperative sputum and in samples collected from the oropharyngeal cavity to identify the causative agent of postoperative complications. The strong correlation between postoperative sputum microbiology and subsequent postoperative infective complications indicates that the oral cavity, pharynx, and hypopharynx rather than the lung itself are the sources of pathogens.

It has been stressed, however, that in esophageal surgery the most obvious route for infection to reach the upper airway is inoculation from the upper alimentary tract (UAT). In the prospective evaluation by Sharp, there was a definite correlation (66% of cases) between pathogens of UAT content collected at operation and those responsible for postoperative infection [63]. Further investigations comparing AWC agents and colonizing agents from UAT are needed to draw definitive conclusions.

7.3. Previous chemoradiotherapy

Some authors have postulated that preoperative chemoradiation increases the risk of postoperative complications [7, 64, 65] with subsequent leucopenia, anorexia, weight loss, and interstitial pneumonitis. It was shown recently that chemoradiotherapy (CRT) leads to immunosuppression by severely impairing the proliferative capacity of T lymphocytes [65]. On the other hand, radiation-induced tissue damage could make the lung parenchyma more vulnerable to postoperative complications and to AWC [64—66]. To the best of our knowledge, no specific data are available on AWC after neo-
adjuvant CRT in lung cancer. Our group has reported the results of a prospective study based on bronchoscopic BAL after neo-adjuvant CRT in esophageal cancer [36]. Our results have confirmed that AWC was present after CRT (30%) and unexpected agents such as CMV could have been encountered.

### 7.4. Preoperative hospital admission

Garibaldi was the first to demonstrate in 1981 that prolonged preoperative hospital stay was an independent factor of postoperative pneumonia among 520 patients submitted for elective thoracic or upper gastrointestinal surgery [67]. Since then, prolonged preoperative hospital stay was frequently suggested as a patient characteristic associated with increased surgical site infection risk [68]. However, length of preoperative stay is likely a surrogate for severity of illness and co-morbid conditions requiring inpatient work-up and/or therapy before the operation. To date, there is no specific data available evaluating the impact of prolonged preoperative admission on AWC.

### Table 3. Literature review of antibiotics prophylaxis in lung cancer surgery. There are nine prospective randomized controlled trials (PRCT) and two large prospective studies tackling the problem with different antibiotic regimens. GTS: general thoracic surgery. POP: postoperative pneumonia. Test of heterogeneity: Chi = 36.6, df: 10, \( p < 0.001 \).

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Postoperative pulmonary complications with first antibiotic prophylaxis</th>
<th>Postoperative pulmonary complications with a second antibiotic prophylaxis</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarka [70]</td>
<td>PRCT</td>
<td>6/60</td>
<td>11/60</td>
<td>0.495</td>
<td>0.17—1.43</td>
</tr>
<tr>
<td>Turna [71]</td>
<td>PRCT</td>
<td>6/50</td>
<td>8/52</td>
<td>0.750</td>
<td>0.24—2.34</td>
</tr>
<tr>
<td>Bernard [72]</td>
<td>PRCT</td>
<td>30/100</td>
<td>15/100</td>
<td>2.429</td>
<td>1.21—4.87</td>
</tr>
<tr>
<td>Wertz [73]</td>
<td>Prospective</td>
<td>4/30</td>
<td>6/30</td>
<td>0.615</td>
<td>0.15—2.45</td>
</tr>
<tr>
<td>Krasnik [74]</td>
<td>PRCT</td>
<td>13/48</td>
<td>8/46</td>
<td>1.764</td>
<td>0.65—4.76</td>
</tr>
<tr>
<td>Olak [75]</td>
<td>PRCT</td>
<td>8/100</td>
<td>7/89</td>
<td>1.019</td>
<td>0.35—2.93</td>
</tr>
<tr>
<td>Aznar [76]</td>
<td>PRCT</td>
<td>3/70</td>
<td>5/57</td>
<td>0.466</td>
<td>0.10—2.03</td>
</tr>
<tr>
<td>Ilves [77]</td>
<td>PRCT</td>
<td>16/118</td>
<td>24/91</td>
<td>0.438</td>
<td>0.21—0.88</td>
</tr>
<tr>
<td>Frimodt-moller [78]</td>
<td>PRCT</td>
<td>18/45</td>
<td>15/47</td>
<td>1.422</td>
<td>0.60—3.34</td>
</tr>
<tr>
<td>Boldt [79]</td>
<td>PRCT</td>
<td>2/60</td>
<td>10/60</td>
<td>0.172</td>
<td>0.036—0.82</td>
</tr>
<tr>
<td>Schussler [80]</td>
<td>Prospective</td>
<td>23/168</td>
<td>8/277</td>
<td>5.334</td>
<td>2.32—12.22</td>
</tr>
<tr>
<td>Total (fixed effects)</td>
<td></td>
<td>129/849</td>
<td>117/909</td>
<td>1.136</td>
<td>0.86—1.49</td>
</tr>
<tr>
<td>Total (random effects)</td>
<td></td>
<td>129/849</td>
<td>117/909</td>
<td>0.975</td>
<td>0.54—1.73</td>
</tr>
</tbody>
</table>

Fig. 3. Meta-analysis of selected studies investigating antibiotics prophylaxis in lung cancer surgery.
8. Antibiotic prophylaxis in lung cancer surgery

Considering that AWC should be a determining element in a broad spectrum of incriminated factors of respiratory failures, its existence raises the question of the accuracy of current antibiotic prophylaxis used in lung cancer surgery. From our literature review summarized in Table 3 and Fig. 3, existing evidence on what constitutes the best appropriate antibiotic prophylaxis in this kind of surgery is poor. To our knowledge, there are nine prospective randomized controlled trials and two large prospective studies tackling the problem with different antibiotic regimens [69–80]. The conclusions that can be reached from these previous studies join the conclusion from Torres [14]: ‘The ideal regime for antibiotic prophylaxis for the prevention of respiratory infections was not discovered and this is still the case 20 years later.’

This is due to several reasons: First, there are no data concerning specifically lung cancer surgery, and all the studies have included a mix of different lung resections, excluding only infectious diseases. Second, basic comparison between first-generation cephalosporin (cefazolin and cefalotin) or penicillin versus placebo has shown no significant difference in terms of pulmonary complications. This argument raises the question of the rationale of targeted antibiotic prophylaxis preventing mainly wound infections in the setting of pulmonary surgery where prevention of respiratory complications is of paramount importance. Third, documented microbiology of postoperative pulmonary complications is restricted to only 5 of the 11 reported studies. Fourth, despite a clear definition of postoperative pneumonia, there is a huge variance in the postoperative incidence of infectious events. This probably emphasizes the differences between surgical team, differences in anesthetic management, and probably the specific local hospital ecology.

However, despite inhomogeneous data, there are significant messages:

(1) AWC detection could act as a clinical based-evidence to target the antibiotic prophylaxis according to specific local ecology. On this basis, every thoracic surgery department should define their specific ecology according to their inherent population. Boldt et al., in 1999, suggested that the best schedule for antibiotic prophylaxis will depend, among other factors, on the bacteria that are present at the time when these patients undergo surgery [79]. They conducted a randomized prospective study in which they compared ampicillin—sulbactam and cephazoline according to their specific local ecology. Every patient was subjected to a preoperative bronchial aspirate through a double-light tube to carry out a microbiological study and determine whether isolated germs were sensitive to the antibiotics used. The isolated microorganisms were mainly H. influenzae, S. pneumoniae, S. viridans, S. aureus, and Klebsiella pneumoniae. Patients from the ampicillin—sulbactam group had significantly fewer pulmonary infections than patients from the cefazolin group. In the first group, all the isolated bacteria were sensitive to the antibiotic used, while in the second group, 8 out of the 25 isolated bacteria were not.

(2) The antibiotic prophylaxis recommended should include not only microorganisms colonizing airways but include also agents from the oropharyngeal cavity. As it has been shown by Sok, the colonization of the airway by pathogens in patients operated for lung cancer resection occurs during the postoperative period via the oral cavity, pharynx, and hypopharynx. Therefore, scheduled prophylaxis administered in the perioperative period would not strictly be applicable to respiratory infections after a lung resection and might include oropharyngeal flora [29]. In France, for example, the recommended antibiotic prophylaxis remains first- or second-generation cephalosporin [81]. This prophylaxis has been shown to decrease the incidence of wound infections and to be effective in the prevention of postoperative empyema. However, it is likely not sufficient to be effective on the broad spectrum required in the prevention of respiratory complications.

(3) Antibiotic prophylaxis should be based on more than one single dose. Bernard et al., in a randomized prospective study on patients subjected to lung surgery, have compared two prophylaxis regimens with cefuroxime [72]. They observed that administration every 6 h for 48 h, as opposed to administration in a single dose, significantly reduced the number of respiratory infections and empyema. By contrast, Olak, comparing the efficacy of two regimens of Cefazolin (single shot vs 48 h) in preventing pulmonary infections in lung-resection surgery, found no significant differences between the two groups [75].

(4) Changing of antibiotic prophylaxis should be well documented by clear prospective and randomized controlled trials avoiding selection and increase of bacterial resistance. Recently, Schussler et al. have reported, in a large sequential study over 18 months, a comparison between first-generation cephalosporin and a short-term (24 h), high-dose (6 g) course of amoxicillin—clavulanate (AC), which targets bacteria most often responsible for preoperative colonization (S. pneumoniae an H. influenzae) [80]. They observed a significant decrease in the incidence of both microbiologically documented and non-documented POP, as well as significant decrease in the overall need of postoperative antibiotics. The authors suggested the use of AC in clinical practice. However, without depicting actual susceptibility results of ‘resistant’ Gram-negative pathogens to both cefamandole and AC, it is not possible to ascertain whether one would have enhanced activity against these pathogens. Because Gram-negative susceptibility varies profoundly among varying geographic areas, the results in one center would be difficult to extrapolate universally.

9. Conclusions

Current evidences on AWCs in patients submitted for lung cancer surgery remain controversial and weak. Their incidence is considered as frequent, estimated between 10% and 83%, but their association with postoperative respiratory infections is unclear. It seems that patients with
AWC are at risk to develop respiratory failures; but if they do, they may develop infection to pathogens related to nosocomial infection. It is likely evident that AWC are more largely dependent on several epidemiologic factors, of the population constituting the country, of local ecology, and of national policy of curative antibiotic treatment. Moreover, AWCs are not limited to bacteria only. Part of the pathogenesis of respiratory failures might be largely influenced by other potential pathogenic microorganisms, especially viral species. Strong limitations continue to preclude to definitive conclusions and every effort should be made to investigate this critical issue.

Therefore, AWC detection should be encouraged whenever possible to target the antibiotic prophylaxis according to specific local ecology. Progress in microbiology cultures and molecular analysis should deserve further information in a near future. We believe that molecular culture-independent techniques applied in the context of AWC will provide, in the future, a great opportunity to discover new and/or emerging pathogens that are currently unknown. Clinicians should keep in mind this old and evident adage: ‘we find only what we are looking for’.

References
