Distribution of Major Pathogens from Sputum and Bronchoalveolar Lavage Fluid in Patients with Noncystic Fibrosis Bronchiectasis: A Systematic Review

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Abstract

Objective: Noncystic fibrosis (non-CF) bronchiectasis remains as a common health problem in Asia. Pathogens’ distribution in airways of patients with non-CF bronchiectasis is important for doctors to make right decision.

Data Sources: We performed this systematic review on the English language literatures from 1966 to July 2014, using various search terms included “pathogens” or “bacteria” or “microbiology” and “bronchiectasis” or “non-cystic fibrosis bronchiectasis” or “non-CF bronchiectasis” or “NCFB.”

Study Selection: We included studies of patients with the confirmed non-CF bronchiectasis for which culture methods were required to sputum or bronchoalveolar lavage fluid (BALF). Weighted mean isolation rates for Haemophilus influenzae, Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis were compared according to different methodology.

Results: The total mean bacterial culture positive rates were 63%. For studies using sputum samples, the mean positive culture rates were 74%. For studies using BALF alone or BALF and sputum, it was 48%. The distributions of main bacterial strains were 29% for H. influenzae, 28% for P. aeruginosa, 11% for S. pneumoniae, 12% for S. aureus, and 8% for M. catarrhalis with methodology of sputum. Meanwhile, the bacterial distributions were 37% for H. influenzae, 8% for P. aeruginosa, 14% for S. pneumoniae, 5% for S. aureus, and 10% for M. catarrhalis with methodology of BALF alone or BALF and sputum. Analysis of the effect of different methodology on the isolation rates revealed some statistically significant differences.

Conclusions: H. influenzae accounted for the highest percentage in different methodology. Our results suggested that the total positive culture rates and the proportion of P. aeruginosa from sputum and BALF specimens had significant differences, which can be used in further appropriate recommendations for the treatment of non-CF bronchiectasis.

Key words: Bronchiectasis; Bronchoalveolar Lavage Fluid; Pathogens; Sputum

Introduction

Bronchiectasis is a heterogeneous and progressive respiratory disease. It is characterized by recurrent cough, sputum production, and recurrent respiratory infections. These patients had chronic colonization or infection of pathogens, the underlying pathological process can be understood as a vicious circle caused by chronic infection.1,2 The two main pathogens isolated have been reported as Haemophilus influenzae (mean of 42% and a range of 29–70%) and Pseudomonas aeruginosa (mean of 18% and range of 12–33%).3 Most studies used sputum culture, mainly as a simple noninvasive and inexpensive procedure, although it may combine with oropharyngeal flora which comes from upper airways. On the contrary, bronchoalveolar lavage fluid (BALF) can avoid oropharyngeal flora and provide bacterial samples of lower airways. Therefore, BALF specimens are the golden standard for evaluating lower airway microorganisms and inflammation in adults.
as well as in young children who are unable to expectorate sputum. Studies using BALF techniques have shown that *H. influenzae* and *P. aeruginosa* may be isolated from 60% to 90% of these patients. Some studies show that 40–67% of children with bronchiectasis have respiratory bacteria pathogens in their sputum with *H. influenzae* and *Streptococcus pneumoniae* as the most commonly bacteria. Stockley et al. achieved sputum of 12 adult bronchiectasis patients found that the most common infecting organisms isolated are *H. influenzae* and *S. pneumoniae*. P. aeruginosa, particularly, tends to be of more amount than *H. influenzae*. A study by Ho indicated that *P. aeruginosa* rank the first followed by *H. influenzae*. Although there are some studies using varying culture methods under different conditions that have obtained the isolation rates of bacteria from the airway of noncystic fibrosis (non-CF) bronchiectasis, previous studies reported various confusing results on the rates of cultural bacteria. It is generally believed that *H. influenzae* account for the highest, but there was a trend toward more *P. aeruginosa* and less *H. influenzae*. And, there was no study making a systematic evaluation and calculation about the proportion of pathogenic bacteria caused by different culture samples. Therefore, the purpose of this study was to find out the real prevalence of pathogens isolated from patients with non-CF bronchiectasis and whether different culture samples would cause different results through a systematic review of the data provided by those enrolled studies.

**Methods**

**Selection of studies**
A retrospective review of the English language literature was performed for inclusion using the following criteria: (1) With the aim of non-CF bronchiectasis patients, and the diagnosis of bronchiectasis was confirmed radiologically by high-resolution computed tomography; (2) The literatures from the period 1966 to 2014 that were restricted to English language literatures and human studies; (3) Articles contained the isolation rates of pathogens. The search included the following databases: PubMed, EMBASE, Web of Science, Cochrane Libray, and Controlled Trials metaRegister. The search terms included “pathogens” or “bacteria” or “microbiology” and “bronchiectasis” or “non-cystic fibrosis bronchiectasis” or “non-CF bronchiectasis” or “NCFB.”

All studies with abstracts that either met the inclusion criteria or did not provide sufficient information were then reviewed for exclusion. Studies were excluded if: (1) Articles were not in the English language; (2) They involved CF bronchiectasis patients; (3) Using either other culture technique such as nasopharyngeal and deep nasal swab; (4) Data could not be extracted by the statistical methods. Also, the references of each article were reviewed for inclusion or exclusion.

**Data extraction**
Basic graphic information was obtained from each studies. Items included culture technique (either sputum or BALF alone or BALF and sputum), median age, sex percentages, the number of patients who had culture performed, the number of patients who had positive culture rates, the isolation rates of the interested pathogens (*H. influenzae*, *P. aeruginosa*, *S. pneumoniae*, *Staphylococcus aureus*, *Moxarella catarrhails*), studies locations, studies years, status, and forced expiratory volume in 1 s (FEV1).

**Statistical analysis**
Studies analyses were conducted by STATA version 12.0 (STATA, College Station, Texas, USA). Culture rates of each specific pathogen were computed per article, such data were pooled and mean isolation rates were weighted according to the different samples. The nonparametric test was performed to determine the statistical differences of specific pathogens isolation rates and positive culture rates between the different samples.

**Results**
The initial search had gained 2848 abstracts or articles. In all, 949 duplicates were removed, 1899 abstracts or articles were screened for eligibility. These articles were evaluated, and after a more full and deeply evaluation, 1856 articles were excluded [Figure 1]. At last, 30 articles were enrolled for final analysis [Table 1]. Among the 30 final articles, 19 articles reported the use of sputum for culture, 8 articles reported BALF results alone, and 4 studies reported BALF and sputum results. Among a total number of 3073 patients, 2358 patients had positive culture results (9 articles did not list the number of positive culture results). The weighted mean positive culture rates of 2358 non-CF bronchiectasis patients was 65% (95% confidence interval [CI]: 55–75%). For sputum samples, mean positive culture rates of 1905 patients was 75% (95% CI: 66–84%). Five hundred and twelve patients using BALF alone or BALF and sputum for culture was 48% (95% CI: 33–63%). Data comparing between the different method of positive culture rates results are shown in Table 2.

**Figure 1:** Flow diagram of the process of selection of included studies. Flow chart depicts the selection process at each stage.
Table 1: Characteristics of and isolation rates in 30 studies of noncystic fibrosis

| Article (year) | Isolation rates (%) | Study years | Status | FEV, (%) (mean) (n) |
|---------------|---------------------|-------------|--------|---------------------|
| Article (year) | Method              | Location    | Age, (years) | Male gender (%) | Total number of patients | Number of positive culture results | Pseudomonas aeruginosa | Haemophilus influenzae | Moraxella catarrhalis | Streptococcus pneumoniae | Staphylococcus aureus | Other pathogens | |
| Pung et al. (1999) | BALF | Hong Kong, China | >18 | 21.7 | 21 | 14 | 19 | 28.6 | – | 4.8 | 14.3 | 28.6 | – | – | |
| Rayner et al. (1994) | Sputum | UK | 51.9 | – | 10 | 9 | 50 | 30 | – | 10 | – | – | – | Stable | 50–60 |
| Ho et al. (1998) | Sputum | Hong Kong, China | 55.1 | 38 | 100 | 65 | 33 | 10 | 2 | 6 | 5 | 9 | – | Stable | 66.59 |
| Tsang et al. (1999) | Sputum | Hong Kong, China | 54.3 | 23.9 | 24 | – | 66.7/76.2 | 12.5/14.3 | – | – | – | 8.39/5 | – | 1996–1997 | Stable | – |
| Pasteur et al. (2000) | BALF | Spain | 52.7 | 37.3 | 146 | 112 | 29 | 35 | 20 | 13 | 14 | 18 | 1996–1997 | – | 74 |
| Angrill et al. (2001) | BALF | Australia | 57.5 | 36.7 | 49 | 22 | 2 | 22.4 | – | 2 | 2 | 24.5 | – | – | 1995–1997 | Stable | 79 |
| Chang et al. (2002) | BALF | Australia | 3.8 | 45.5 | 33 | 11 | – | 72.7 | 3 | 9 | – | 9 | – | Stable | 65 (10) |
| Puharic et al. (2002) | Sputum | Thailand | 58 | – | 50 | 41 | 20 | 14 | 4 | 6 | – | 38 | 1999–2001 | – | 71.9 (30) |
| Angrill et al. (2002) | BALF | France | 58 | 34 | 42/59 | 22/33 | 9/12 | 6/32 | 5/– | 7/14 | –3/– | 6/12 | 1998–1999 | Stable | 75 |
| Edwards et al. (2003) | Sputum | New Zealand | 10 | 60 | 60 | 40 | 2 | 68 | 6 | 12 | – | 12 | 1998–2000 | – | 69 (39) |
| Davies and Wilson (2004) | Sputum | UK | 51.9 | 33.3 | 35 | 22 | 22.9 | 17.1 | 2.9 | – | 17.1 | 5.7 | – | 1998–2000 | – | – |
| Eastham et al. (2004) | Sputum | Spain | 1.1 | 66.7 | 93 | – | 6 | 48 | 17 | 22 | 8 | 12 | 1999–2002 | – | – |
| Lai et al. (2004) | Sputum | Taiwan, China | 11 | 41.4 | 29 | 12 | 25/21.4 | 16.7/14.3 | – | 16.7/14.3 | – | 50/42.9 | 1996–2002 | – | 67.6 (13) |
| Karadag et al. (2005) | Sputum | Turkey | 7.4 | 50.5 | 111 | 65 | 10.8 | 38.5 | 6.2 | 23 | 16.9 | 4.6 | 1991–2001 | – | 65–75.4 |
| Li et al. (2005) | Sputum | China | 12.1 | 47.8 | 136 | – | 11/14.4 | 39/51 | 2/3 | 17/22.1 | 4/8 | 8/10.6 | 1987–2001 | – | 71 |
| Benjair (2007) | Sputum | Saudi Arabia | – | 49.7 | 151 | – | 16 | 37 | – | 17 | – | – | 1986–2002 | – | – |
| Martin et al. (2007) | Sputum | Spain | 69.9 | 48.7 | 76 | – | 19.7 | 18.4 | – | – | – | – | 1993–2005 | Stable | 59.04 |
| Kapyari et al. (2009) | Sputum | Spain | 5.5 | 56.7 | 27 | 13 | 11.1 | 25.9 | 7.4 | 11.1 | 7.4 | – | 2003–2005 | Stable | 82.5 |
| Hare et al. (2010) | BALF | Australia | 2.3 | 66.7 | 45 | 26 | – | 47 | 20 | 18 | 4 | – | 1997–2002 | – | – |
| Macfarlane et al. (2010) | Sputum | UK | 60.6 | 38.5 | 143 | 114 | 43 | 52 | 27 | 34 | 24 | 58 | 2007–2009 | – | – |
| Kapoor et al. (2012) | BALF | Australia | 5.25 | 56.6 | 113 | 77 | 6 | 47 | 10 | 22 | 12 | 7 | 1987–2009 | – | – |
| Murray et al. (2011) | Sputum | Scotland | 61 | 42.1 | 57 | 57 | 42.1 | 45.6 | 3.5 | 1.8 | 5.3 | 1.8 | 1992–2009 | Stable | 63.4–72.9 |
| Sahabudeen and Smith (2011) | Sputum | UK | 64.5 | 36.7 | 158 | 135 | 26.6 | 13.9 | 3.8 | 7 | 1.9 | 16.6 | 2007–2009 | – | – |
| Chalmers et al. (2012) | Sputum | UK | 67 | 42.9 | 385 | 290 | 21 | 38.6 | 11.4 | 9.7 | 12.4 | 9.3 | – | Stable | 69.2 |
| Hare et al. (2013) | BALF | Australia | 2.38 | 61.5 | 104 | – | – | 31 | 12 | 16 | – | – | 2007–2011 | – | – |
| Smith et al. (2014) | Sputum | Australia | 60 | 50 | 8 | – | 75/66.7 | 13/11.1 | – | – | – | 25/22.2 | 2007–2009 | – | 33 |
| Wilson et al. (2013) | Sputum | Australia, Germany, spain, Sweden, UK, USA | 63 | 33.9 | 124 | – | 54/42.9 | 24.2/19.2 | 6/5.5 | 7/3.5 | 8/2.16 | 13/7.10.9 | 2007–2011 | – | 54.6–57.2 |
| Rogers et al. (2013) | Sputum | UK | 62.9 | 31.7 | 41 | – | 27 | 29 | – | – | – | – | 2009–2010 | Stable | 72.9 |
| Pratelli et al. (2013) | BALF | Australia | 2.2 | 57.1 | 136 | 26 | 7.1 | 28.6 | 16.1 | 17.9 | – | – | – | Stable | – |
| Chalmers et al. (2014) | BALF | UK | 27 | 608 | 440 | 11.5 | 29.1 | 10.4 | 6 | 7 | 7.9 | 2011–2012 | Stable | – | – |

The number of patients do the lung function. BALF: Bronchoalveolar lavage fluid; FEV, Forced expiratory volume in 1 s.
Thirty articles were weighted mean values for analyses of the isolation rates of the 5 major pathogens. Nineteen articles reported *H. influenzae* from sputum samples, the mean isolation rate was 29% (95% CI: 23–36%), 12 articles reported using BALF alone or BALF and sputum method and the mean isolation rate was 37% (95% CI: 29–44%). For *P. aeruginosa*, 19 articles using sputum method and mean isolation rate was 28% (95% CI: 21–34%), 9 articles using BALF alone or BALF and sputum method and mean isolation rate was 8% (95% CI: 5–11%) [Table 3]. For *S. pneumoniae*, 14 articles reported mean isolation rate as 11% (95% CI: 7–14%) by sputum culture, 12 articles using BALF alone or BALF and sputum method was 14% (95% CI: 9–19%). Ten articles of mean isolation rate cultured from sputum for *S. aureus* was 12% (95% CI: 7–16%), 8 articles with BALF or BALF and sputum results was 5% (95% CI: 3–6%) [Table 3]. Thirteen articles reported mean isolation rate cultured from sputum for *Moxarella catarrhals* was 8% (95% CI: 5–11%), 8 articles with BALF or BALF and sputum results was 10% (95% CI: 5–15%) [Table 3].

Analyses were performed to determine whether isolation rates were affected by the two different methods of culture performed [Table 3]. The isolation rates of five major pathogens except *P. aeruginosa* had no significant statistical difference. While *P. aeruginosa* was isolated more frequently in studies using sputum than those using BALF or BALF and sputum for culture (28% vs. 8%; *P* = 0.004). We also analyzed whether there are some statistical differences between major pathogens rates using two different methods among adults and children. Results of this analysis showed *P. aeruginosa* has a significant statistical difference among adults and children in sputum samples (33% vs. 6%; *P* = 0.029), while other four isolation rates of pathogens have no statistical difference.

**Discussion**

The characteristics of bronchiectasis are progressive inflammation and a cycle of worsening pulmonary damage. As a long-term disease which is hard to clear, appropriate further treatments and antibiotics use on bronchiectasis should be based on the exact prevalence percentages of pathogens. However, the microbiology of bronchiectasis varies among in different studies. This meta-analysis summarized and analyzed 30 articles of pathogens of non-CF bronchiectasis. Our results showed that *H. influenzae* accounted for the highest percentage in two kinds of culture methods. Sputum and BALF specimens suggested that the total positive culture rates and the proportion of *P. aeruginosa* had significant differences. Total positive culture rates in sputum specimens were higher than those in BALF specimens, which revealed that the results from sputum may combine with oropharyngeal flora from upper airways, as BALF are the golden standard for evaluating lower airway microorganisms and inflammation.[4]

King conducted several studies showing that *H. influenzae* ranked the first common pathogen (range: 29–70%), *P. aeruginosa* followed as range of 12–31%.[37] While Shah et al. found that 32% for *H. influenzae*, 14% for *S. pneumoniae*, 8% for *M. catarrhals*, 5% for *S. aureus*, and 2% for *P. aeruginosa*. Some studies of sputum microbiology and bronchoscopic sampling revealed that *S. aureus* occurred in non-CF bronchiectasis patients of 4–10%.[38] Stockley et al. found that the most common infected organisms isolated are *H. influenzae* and *S. pneumoniae*. In our study, the mean isolation rates was 29% for *H. influenzae*, 28% for *P. aeruginosa* by using sputum, which were in accordance with King’s results. We found 11% for *S. pneumoniae*, 12% for *S. aureus*, and 8% for *M. catarrhals*, which were similar with Shah study except the isolate rates of *P. aeruginosa*, which focused on children. Our study explored whether there were statistical differences between major pathogens rates by using two different methods among adults and children. Results of this analysis showed that *P. aeruginosa* had a significant statistical difference among adults and children, while other four isolation rates of pathogens did not. This result

### Table 2: Percentages of patients who had positive culture results

| Variables | All | Sputum | BALF alone or BALF and sputum | P     |
|-----------|-----|--------|-------------------------------|-------|
| Rate of positive culture results (95% CI) | 0.65 (0.55–0.75) | 0.75 (0.66–0.84) | 0.48 (0.33–0.63) | 0.000 |
| Number of studies | 21 | 13 | 9 |       |
| Number of patients who had culture performed | 2358 | 1905 | 512 |       |

*P* value with respect to the difference of the rate of positive culture results for studies that used sputum and for studies that used BALF alone or BALF and sputum, calculated by nonparametric test. BALF: Bronchoalveolar lavage fluid; CI: Confidence interval.

### Table 3: Weighted mean isolation rates according to the culture technique used in the studies

| Pathogens             | Sputum | BALF alone or BALF and sputum | P     |
|-----------------------|--------|-------------------------------|-------|
| *Haemophilus influenza* | n = 19 | n = 12                        |       |
| Isolation rate (95% CI) | 0.29 (0.23–0.36) | 0.37 (0.29–0.44) | 0.172 |
| *Pseudomonas aeruginosa* | n = 19 | n = 9                  |       |
| Isolation rate (95% CI) | 0.28 (0.21–0.34) | 0.08 (0.05–0.11) | 0.004 |
| *Streptococcus pneumoniae* | n = 14 | n = 12               |       |
| Isolation rate (95% CI) | 0.11 (0.07–0.14) | 0.14 (0.09–0.19) | 0.205 |
| *Staphylococcus aureus* | n = 10 | n = 8              |       |
| Isolation rate (95% CI) | 0.12 (0.07–0.16) | 0.05 (0.03–0.06) | 0.093 |
| *Moxarella catarrhals* | n = 13 | n = 8              |       |
| Isolation rate (95% CI) | 0.08 (0.05–0.11) | 0.10 (0.05–0.15) | 0.473 |

*P* values comparing the pathogen isolation rate for studies that used sputum with studies that used BALF or sputum, calculated by nonparametric test. BALF: Bronchoalveolar lavage fluid; n: Numbers of studies; CI: Confidence interval.
can best interpret Shah’s study that *P. aeruginosa* rate was lower in children. Clinically, patients with *P. aeruginosa* infected in non-CF bronchiectasis would bring about a more rapid decline in lung function and earlier mortality.\(^2\) Hence, more attention should be paid to *P. aeruginosa*. Recommendations for antibiotic therapy for non-CF bronchiectasis are periodically reviewed and updated by the British Thoracic Society.\(^1\) These recommended uses were combination of antibiotics not required in patients colonized with *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *S. pneumoniae*. In patients with *P. aeruginosa*, who are sensitive to ciprofloxacin, monotherapy with oral ciprofloxacin can be used as a first-line treatment.

In this study, we extracted FEV\(_1\), data from the included articles. Articles that only part of patients did lung function in a study or did not provide any data on lung function were excluded. Then we divided the patients involved into three groups, <50%, 50–73%, and more than 73%, respectively. There was no obvious difference in the distribution of pathogens, which may be due to the relatively small number of sample, or the different health states of the patients. We revealed that *S. aureus* is increasing compared to the previous studies. Our study also found the positive culture rates of different methods had the obvious statistical difference (74% vs. 48%, \(P = 0.000\)). However, the isolation rates of four pathogens excepted *P. aeruginosa* (28% vs. 8%) using different methods have no statistical difference.

This study, like any systematic reviews, is limited by pool potential heterogeneous data. The included articles resulted from different countries, patients may have different races or may have different medical resources and conditions or some patients may obtain antibiotics before the study although there is no evidence showing that using antibiotics would change bacteria distribution. As a result, data derived from these studies may not actually show the true prevalence of five major pathogens in non-CF bronchiectasis.

**Conclusions**

The data suggest that *H. influenzae* ranks the first as a major pathogen in non-CF bronchiectasis, followed by *P. aeruginosa*, *S. pneumoniae*, *S. aureus*, and *M. catarrhalis*. Methods using sputum or BALF have some statistical differences. The treatment of non-CF bronchiectasis patients may be according with the prevalence data from this study.

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**Conflicts of interest**

There are no conflicts of interest.

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