Review Article

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*, *Stapylococcus aureus*, *Moxarella catarrhails* 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. catarrhails* 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. catarrhails* 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

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.167360

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Received: 15-04-2015 **Edited by:** Li-Shao Guo

How to cite this article: Miao XY, Ji XB, Lu HW, Yang JW, Xu JF. Distribution of Major Pathogens from Sputum and Bronchoalveolar Lavage Fluid in Patients with Noncystic Fibrosis Bronchiectasis: A Systematic Review. Chin Med J 2015;128:2792-7.

as well as in young children who are unable to expectorate sputum.[4] Studies using BALF techniques have shown that *H. influenzae* and *P. aeruginosa* may be isolated from 60% to 90% of these patients.[5]

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.[6,7] Stockley *et al*. achieved sputum of 12 adult bronchiectasis patients found that the most common infecting organisms isolated are *H. influenzae* and *S. pneumoniae*.[8] *P. aeruginosa*, particulaly, tends to be of more amount than *H. influenzae*. A study by Ho indicated that *P. aeruginosa* rank the first followed by *H. influenza*.[9]

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*, *Stapylococcus aureus*, *Moxarella catarrhails*), studies locations, studies years, status, and forced expiratory volume in 1 s (FEV_1).

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.

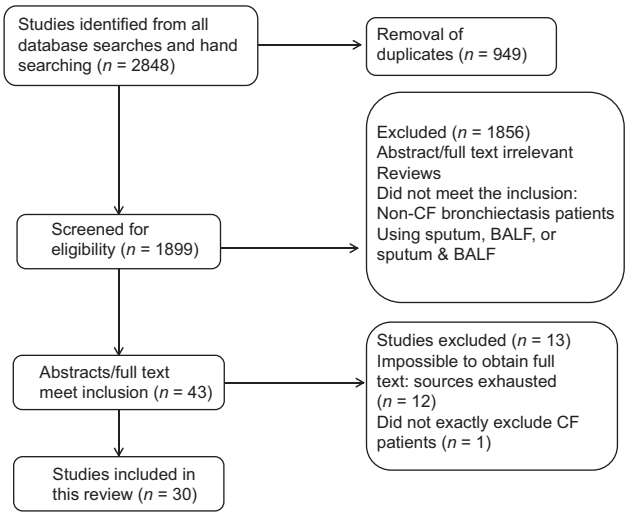

Figure 1: Flow diagram of the process of selection of included studies. Flow chart depicts the selection process at each stage.

Table 1: Characteristics of and isolation rates in 30 studies of noncystic fibrosis

Article (year)	Collect method	Location	Age, mean (years)	Male gender (%)	Total number of patients	Number of positive culture results	Isolation rates (%)						Study years	Status	FEV_1 (%) (mean) (*n*)
							Pseudomonas aeruginosa	*Haemophilus influenzae*	*Moraxella catarrhalis*	*Streptococcus pneumoniae*	*Staphylococcus aureus*	Other pathogens			
Pang *et al.* (1989)[10]	BALF	Hong Kong, China	>18	21.7	21	14	19	28.6	–	4.8	14.3	28.6	–	–	–
Rayner *et al.* (1994)[11]	Sputum	UK	51.9	–	10	9	50	30	–	10	–	–	–	Stable	50–60
Ho *et al.* (1998)[9]	Sputum	Hong Kong, China	55.1	38	100	65	33	10	2	6	5	9	–	Stable	66.59
Tsang *et al.* (1999)[12]	Sputum	Hong Kong, China	54.3	23.9	24	–	66.7/76.2	12.5/14.3	–	–	–	8.3/9.5	1996–1997	Stable	–
Pasteur *et al.* (2000)[13]	Sputum	UK	52.7	37.3	146	112	29	35	20	13	14	18	1996–1997	–	74
Angrill *et al.* (2001)[14]	BALF	Spain	57	36.7	49	22	2	22.4	–	2	2	24.5	1995–1997	Stable	79
Chang *et al.* (2002)[15]	BALF	Australia	3.8	45.5	33	11	–	72.7	3	9	–	9	–	Stable	65 (10)
Palwatwichai *et al.* (2002)[16]	Sputum	Thailand	58	–	50	41	20	14	4	6	–	38	1999–2001	–	71.9 (30)
Angrill *et al.* (2002)[17]	Sputum/ BALF	Spain	58	34	42/59	22/33	9/12	26/32	5/–	7/14	–/3	6/12	1998–1999	Stable	75
Edwards *et al.* (2003)[7]	Sputum	New Zealand	10	60	60	40	2	68	6	12	–	12	1998–2000	–	69 (39)
Davies and Wilson (2004)[18]	Sputum	UK	51.9	33.3	35	22	22.9	17.1	2.9	–	17.1	5.7	1998–2000	–	–
Eastham *et al.* (2004)[19]	Sputum and BALF	UK	1.1	66.7	93	–	6	48	17	22	8	12	1999–2002	–	–
Lai *et al.* (2004)[20]	Sputum and BALF	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)[6]	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)[21]	Sputum and BALF	UK	12.1	47.8	136	–	11/14.4	39/51	2/3	17/22.1	4/4.8	8/10.6	1987–2001	–	71
Banjar (2007)[22]	Sputum	Saudi Arabia	–	49.7	151	–	16	37	–	17	–	–	1986–2002	–	–
Martínez-García *et al.* (2007)[23]	Sputum	Spain	69.9	48.7	76	–	19.7	18.4	–	–	–	–	1993–2005	Stable	59.04
Kapur *et al.* (2009)[24]	Sputum and BALF	Australia	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)[25]	BALF	Australia	2.3	66.7	45	26	–	47	20	18	4	–	1997–2002	–	–
Macfarlane *et al.* (2010)[26]	Sputum	UK	60.6	38.5	143	114	43	52	27	34	24	58	2007–2009	–	–
Kapur *et al.* (2012)[27]	BALF	Australia	5.25	56.6	113	77	6	47	10	22	12	7	1987–2009	–	–
Murray *et al.* (2011)[28]	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)[29]	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)[30]	Sputum	UK	67	42.9	385	290	21	38.6	11.4	9.7	12.4	9.3	–	Stable	69.2
Hare *et al.* (2012)[31]	BALF	Australia	2.38	61.5	104	–	–	31	12	16	–	–	2007–2011	–	–
Smith *et al.* (2014)[32]	Sputum	Australia	60	50	8	–	75/66.7	13/11.1	–	–	–	25/22.2	2007–2009	–	33
Wilson *et al.* (2013)[33]	Sputum	Australia, Germany, spain, Sweden, UK, USA	63	33.9	124	–	54/42.9	24.2/19.2	6.5/5.1	7.3/5.8	20.2/16	13.7/10.9	2007–2011	–	54.6–57.2
Rogers *et al.* (2013)[34]	Sputum	UK	62.9	31.7	41	–	27	29	–	–	–	–	2009–2010	Stable	72.9
Pizzutto *et al.* (2013)[35]	BALF	Australia	2.2	57.1	136	26	7.1	28.6	16.1	17.9	–	–	–	Stable	–
Chalmers *et al.* (2014)[36]	Sputum	UK	–	40	608	440	11.5	29.1	10.4	6	7	7.9	2011–2012	Stable	–

The number of *n* represent part do the lung function. BALF: Bronchoalveolar lavage fluid; FEV_1: 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. pneumonia*, 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 catarrhalis* was 8% (95% *CI*: 5–11%), 8 articles with BALF or BALF and sputum results was 10% (95% *CI*: 5–15%) [Table 3].

Table 2: Percentages of patients who had positive culture results

Variables	Studies			*P*
	All	Sputum	BALF alone or BALF and sputum	
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 between 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 influenzae	*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 catarrhalis	*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 BALF and sputum, calculated by nonparametric test. BALF: Bronchoalveolar lavage fluid; *n*: Numbers of studies; *CI*: Confidence interval.

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 brochiectasis 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. catarrhails*, 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. catarrhalis*, 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

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.

Financial support and sponsorship

This work was supported by grants from the National Natural Science Foundation of China (Nos. 81170003, 81370109), Science and Technology Commission of Shanghai Municipality (Nos. 134119a6400, 12JC1402300) and Shanghai Municipal Education Commission (No. 13SG21).

Conflicts of interest

There are no conflicts of interest.

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