SURVEY OF BACTERIAL CAUSES OF LUNG INFECTION IN NON-CYSTIC FIBROSIS BRONCHIECTASIS IN THAILAND

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Abstract. Bronchiectasis can predispose patients to lung infections. In this study, the primary aim was to determine the etiology of lung infection among non-cystic fibrosis bronchiectasis patients and the secondary aim was to identify factors associated with *Pseudomonas aeruginosa* infection in order to inform empiric treatment of these patients and guide efforts to prevent *Pseudomonas aeruginosa* infection among these patients at the study hospital. We retrospectively reviewed the charts of non-cystic fibrosis bronchiectasis patients with an episode of infection who presented to Srinagarind Hospital, Khon Kaen Province, Thailand during 2011-2016. Demographic data, sputum culture results and chest radiograph results were recorded. A total of 144 patients were included in this study. The mean [± standard deviation (SD)] age of subjects was 65 (±14.4) years; 57.6% male. Of the 144 subjects, 18 (12.5%) had no growth on sputum culture, 71 (49.3%) grew normal throat flora and 55 (38.2%) grew out a potential pathogen. These pathogens consisted of *Pseudomonas aeruginosa* (n = 19, 13.2%), *Klebsiella pneumoniae* (n = 9, 6.3%), *Escherichia coli* (n = 6, 4.2%), and *Staphylococcus aureus* (n = 5, 3.5%). Factors significantly associated with *Pseudomonas aeruginosa* infection were: female gender (odds ratio (OR): 7.1; 95% confident interval (CI): 1.9-26.6; p=0.004), having had a prior history of pulmonary tuberculosis (OR: 5.9; 95%CI: 1.4-24.2; p=0.015) and taking N-acetylcysteine (OR: 4.7; 95%CI: 1.1-19.4; p=0.033). In our study, we identified a potential pathogen in 38.2% of subjects. *P. aeruginosa* was the most common pathogen isolated and its infection was associated with female gender, prior history of pulmonary tuberculosis and use of N-acetylcysteine. These data can guide management of these subjects at the study institution.

Keywords: bronchiectasis, *Pseudomonas aeruginosa*, lung infection

INTRODUCTION

Non-cystic fibrosis bronchiectasis is a chronic airway disease associated with impaired phlegm clearance predisposing to frequent lung infections and colonization with pathogens. (Goeminne and Dupont, 2010; Pasteur *et al*, 2010). Symptoms of bronchiectasis

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include chronic cough, tenacious sputum production, hemoptysis, and dyspnea that usually worsens during an episode of infection (Baydarian and Walter, 2008). Frequent infections decrease quality of life, increase the need for hospitalization and increase mortality risk (McShane *et al*, 2013).

Patients with bronchiectasis are more likely to be colonized with both potentially pathogenic microorganisms (PPMs) and non-potentially pathogenic microorganisms (NPPMs) (Cabello *et al*, 1997). Both PPMs and NPPMs can cause lung infection in bronchiectasis patients (Cabello *et al*, 1997; Cole, 1986). Commonly reported PPMs in bronchiectasis patients include: *Pseudomonas aeruginosa, Haemophilus* spp, *Streptococcal pneumoniae, Staphylococcus aureus* and *Moraxella catarrhalis*. NPPMs reported include *Streptococcus viridian, Enterobacter, Corynebacterium, Neisseria* spp and coagulase-negative *Staphylococcus* (Angrill *et al*, 2002; Cabello *et al*, 1997). Previous studies have reported the most common microorganism isolated in patients with bronchiectasis is *P. aeruginosa* (Borekci *et al*, 2016; Chawla *et al*, 2015; Dimakou *et al*, 2016; Palwatwichai *et al*, 2002). Bronchiectasis patients with chest infection should receive antimicrobial therapy covering *P. aeruginosa* (Feldman, 2011). Previously reported risk factors for *P. aeruginosa* in sputum included older age, previous corticosteroid use, history of frequent episodes of infection and poor lung function (Angrill *et al*, 2002; Chawla *et al*, 2015; Guan *et al*, 2014). Some previous studies have reported isolating other microorganisms, such as a study from Spain that reported the most common microorganism isolated was *Haemophilus influenzae* (Angrill *et al*, 2002).

The aims of this study were to identify the microorganisms causing infected bronchiectasis in Thai patients with non-cystic fibrosis bronchiectasis and evaluate the factors associated with *P. aeruginosa* infection, in order to guide empiric treatment.

MATERIALS AND METHODS

We conducted this retrospective cohort study among patients with non-cystic fibrosis bronchiectasis who presented to Srinagarind Hospital, Khon Kaen Province, Thailand from January 2011 to October 2016. This study was approved by the Khon Kaen Institutional Ethics Committee (HE-581450). We retrospectively reviewed the charts of non-cystic fibrosis bronchiectasis patients aged ≥18 years clinically diagnosed with lung infection defined as a change in one or more of the general symptoms of bronchiectasis: increasing amount of sputum or purulent sputum, worsening dyspnea, increasing cough, having new onset fever or developing hemoptysis (Pasteur *et al*, 2010). Patients with malignancies, immunocompromised patients, such as those with HIV infection, organ transplant and patients using immunosuppressive medications were excluded from this study. Demographic data, radiographic findings and spirometry results were recorded. Sputum cultures used for this study were the first collected sputum culture, if the patient had more than one culture specimen. Quantitative data are reported as means (± standard deviation (SD)) and qualitative data are reported as percentages. Univariate logistic regression analysis was used to evaluate the factors associated with *P. aeruginosa* infection. Stepwise backward multiple logistic regression analysis was used to analyze the factors with a p-value <0.20 on univariate analysis or

factors with previous reports of clinical significance. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated. A p-value <0.05 was considered statistically significant. All data were analyzed using STATA version 11 (STATA Statistical Software, College Station, TX).

RESULTS

A total of 144 subjects were included in this study. The demographic data are shown in Table 1. The mean (±SD) age of subjects was 65.1 (±14.4) years; 57.6% male (n = 83). Seventy patients (45.1%) were former smokers and 9

Table 1
Demographic characteristics of study subjects (n = 144).

Characteristics	n (%)
Mean (SD) age in years	65.1 (14.4)
Male	83 (57.6)
Smoking history	
Non-smoker	70 (48.6)
Former smoker	65 (45.1)
Current smoker	9 (6.3)
Symptoms	
Cough	140 (97.2)
Sputum production	136 (94.4)
Dyspnea	113 (78.5)
Fever	73 (50.7)
Non-massive hemoptysis	34 (23.6)
Massive hemoptysis	29 (20.1)
Wheezing	5 (3.5)
Comorbid diseases	
Hypertension	60 (41.7)
Diabetes mellitus	23 (16)
Rheumatoid arthritis	5 (3.5)
Chronic kidney disease	5 (3.5)
Coronary heart disease	1 (0.7)
History of pulmonary tuberculosis	91 (63.2)
Antibiotic use in the previous 90 days	47 (32.6)
Destroyed lung	5 (3.5)
Number of previous infected bronchiectasis episode	
None	106 (73.6)
Once	28 (19.4)
Twice	9 (6.3)
≥ 3 times	1 (0.7)
Long term medication use	
Short acting beta-2 agonist	71 (49.3)
Inhale corticosteroid / long acting beta-2 agonist	40 (27.8)
N-acetylcysteine	31 (21.5)
Long term antibiotic use	9 (6.3)

SD: standard deviation

(6.3%) were current smokers. Ninety-one subjects (63.2%) had a prior history of pulmonary tuberculosis. The most common presenting symptom reported was cough (n = 140, 97.2%), followed by increased sputum production (n = 136, 94.4%), dyspnea (n = 113, 78.5%), fever (n = 73, 50.7%), non-massive hemoptysis (n = 34, 23.6%), massive hemoptysis (n = 29, 20.1%) and wheezing (n = 5, 3.5%). Sixty patients (41.7%) had hypertension and 23 (16%) had diabetes mellitus. Forty-seven patients (32.6%) had a history of antibiotic use during the previous 90 days. Seventy-one patients (49.3%) had used a short-acting beta-2 agonist (SABA), 40 (27.8%) had used an inhaled corticosteroid along with a long acting bronchodilator (ICS-LABA) and 31 (21.5%) had used N-acetylcysteine. Nine subjects (6.3%) were prescribed long term antibiotics. On chest radiography, a destroyed lung, defined as total destruction of one lung, was found in 5 patients (3.5%). Spirometry was performed in 19 patients (13.2%). The mean (±SD) pre-bronchodilator percent predicted forced vital capacity (FVC), percent predicted forced expiratory volume in one second (FEV1) and FEV1/FVC ratio were 65.3 (±13.4)%, 62.1 (±15.4)% and 0.64 (0.15). Twelve of these 19 patients with pulmonary function testing results (63.2%) had an obstructive pattern on spirometry.

Table 2
Culture results among study subjects (n = 144).

Culture results	n (%)
No growth	18 (12.5)
Normal flora	71 (49.3)
Potential pathogens isolated	55 (38.2)
Pseudomonas aeruginosa	19 (13.2)
Klebsiella pneumoniae	9 (6.3)
Escherichia coli	6 (4.2)
Staphylococcus aureus	5 (3.5)
Acinetobacter baumannii	4 (2.8)
Stenotrophomonas maltophilia	4 (2.8)
Proteus spp	3 (2.1)
Haemophilus influenzae	2 (1.4)
Moraxellla catarrhalis	1 (0.7)
Burkholderia pseudomallei	1 (0.7)
Serratia marcescens	1 (0.7)

The sputum culture results are shown in Table 2. Eighteen patients (12.5 %) had no growth on the sputum culture, 71 (49.3%) grew normal throat flora and 55 (38.2%) grew potential pathogens consisting of *Pseudomonas aeruginosa* (n = 19, 13.2%), *Klebsiella pneumoniae* (n = 9, 6.3%), *Escherichia coli* (n = 6, 4.2%), *Staphylococcus aureus* (n = 5, 3.5%), *Acinetobacter baumannii* (n = 4, 2.8%), *Stenotrophomonas maltophilia* (n = 4, 2.8%), *Proteus* spp (n = 3, 2.1%), *Haemophilus influenzae* (n = 2, 1.4%), *Moraxellla catarrhalis* (n = 1, 0.7%), *Burkholderia pseudomallei* (n = 1, 0.7%) and *Serratia marcescens* (n = 1, 0.7%).

Nineteen patients (13.2%) had *Pseudomonas aeruginosa* infection. Factors significantly associated with *P. aeruginosa* infection on univariate analysis were: prior history of pulmonary tuberculosis, N-acetylcysteine use and short acting beta-2 agonist use (Table 3). Factors significantly associated with *P. aeruginosa* infection on multivariate analysis were: female gender (adjusted OR: 7.08; 95% CI: 1.88-26.57; p=0.004), having a prior history of pulmonary tuberculosis (adjusted OR: 5.85; 95% CI: 1.40-24.41; p=0.015) and using N-acetylcysteine (adjusted OR: 4.69; 95% CI: 1.14-19.36; p=0.033) (Table 4).

DISCUSSION

In our study, the majority of subjects

Table 3
Factors associated with *Pseudomonas aeruginosa* infection analyzed by univariate logistic regression analysis.

Factors	Pseudomonas isolated (*n*=19)	No Pseudomonas Isolated (*n*=125)	OR (95%CI)	*p*-value
Mean (SD) age in years	66.6 (8.7)	64.8 (15.1)	1.01 (0.97-1.04)	0.613
Female gender	12 (63.2%)	49 (39.2%)	2.66 (0.98-7.22)	0.050
History of pulmonary tuberculosis	16 (84.2%)	75 (60%)	3.56 (0.98-12.84)	0.031
Antibiotic use in the previous 90 days	4 (21.1%)	43 (34.4%)	0.51 (0.16-1.63)	0.232
Previous infected bronchiectasis episode	3 (15.8%)	35 (28%)	0.48 (0.13-1.76)	0.239
Hemoptysis	6 (31.6%)	52 (41.6%)	0.65 (0.23-1.82)	0.401
Destroy lung	1 (5.3%)	4 (3.2%)	1.68 (0.18-15.89)	0.666
Diabetes mellitus	2 (10.5%)	21 (16.8%)	0.58 (0.13-2.71)	0.467
Inhale corticosteroid use	8 (42.1%)	32 (25.6%)	2.11 (0.78-5.72)	0.148
Long-term antibiotics use	1 (5.3%)	8 (6.4%)	0.81 (0.10-6.89)	0.845
N-acetylcysteine use	8 (42.1%)	23 (18.4%)	3.23 (1.17-8.92)	0.029
Short acting beta-2 agonist use	14 (73.7%)	57 (45.6%)	3.34 (1.13-9.84)	0.020

OR: odds ratio; CI: confident interval.

Table 4
Factors associated with *Pseudomonas aeruginosa* infection analyzed by multivariable logistic regression analyzed with stepwise backward selection.

Factors	Adjusted OR (95%CI)	p-value
Female gender	7.08 (1.88-26.57)	0.004
History of pulmonary tuberculosis	5.85 (1.40-24.41)	0.015
N-acetylcysteine use	4.69 (1.14-19.36)	0.033
Short acting beta-2 agonist use	4.02 (0.98-16.49)	0.053
Previous infected bronchiectasis episode	0.39 (0.09-1.66)	0.204
Antibiotic use in the previous 90 days	0.30 (0.07-1.19)	0.086
Diabetes mellitus	0.27 (0.05-1.64)	0.157

OR: odds ratio; CI: confident interval

were male, unlike the results of previous studies (Aksamit *et al*, 2017; Dimakou *et al*, 2016; Morrissey and Harper, 2004; Palwatwichai *et al*, 2002; Raghavan and Jain, 2016; Vidaillac *et al*, 2018). This may be due to differences in the study population and subject selection processes. In the Asia-Pacific the most common cause of bronchiectasis is tuberculosis, whereas in Europe and North America the most common etiologies of bronchiectasis are non-tuberculosis mycobacterial (NTM) infection, cystic fibrosis, auto-immune diseases and immunodeficiency (Chandrasekaran *et al*, 2018; Kwak *et al*, 2010; Redondo *et al*, 2016). Thailand is endemic for tuberculosis, which is more common in males (Jittimanee *et al*, 2009) while auto-immune disease and NTM infection are more common in females (Lonni *et al*, 2015). Sixty percent of study subjects had a prior history of pulmonary tuberculosis.

Bronchiectasis patients often experience multiple episodes of infection with symptoms of fever, worsening cough, dyspnea, increased production of sputum, production of purulent of sputum and hemoptysis which often required a course of antibiotic (Pasteur *et al*, 2010). Sputum cultures can guide treatment. However, in our study, fewer than 40% of subjects had a sputum culture revealing a potential pathogen. This percentage can be increased by performing an invasive procedure, such as bronchoscopy with bronchial brushings or bronchoalveolar lavage (Angrill *et al*, 2002; Chawla *et al*, 2015), but this aggressive approach is expensive, may not be easily available in some institutions and the patient may not tolerate the procedure or may not be able to afford it.

In our study, *P. aeruginosa* was the most commonly isolated organism, similar to the findings from other studies (Chawla *et al*, 2015; Palwatwichai *et al*, 2002; Wilson *et al*, 1997). However, in some other studies *Haemophilus influenzae* was the most common organism isolated (Angrill *et al*, 2002; King *et al*, 2007; Li *et al*, 2005). This difference may be due to variations in pathogens by locations. This may also be due to the organisms found in various institutions and how long the patient was in that institution before the specimen was collected. It may also be due to patient factors, such as their immune status.

P.aeruginosa infection is associated with poorer pulmonary function, higher hospitalization rates and greater morbidity and mortality (Wang *et al*, 2018). *P. aeruginosa* colonization can also provoke intense inflammation resulting in unfavorable lung function test results (Guan *et al*, 2015a; Guan *et al*, 2015b; Ho *et al*, 1998). Previously reported factors significantly associated with *P. aeruginosa* infection include older patient age, greater extent of bronchiectasis seen on chest radiography or high-resolution computed tomography (HRCT), more frequent episodes of infections, previous corticosteroid usage, greater number of hospital admissions, prolonged hospital stay and poor lung function (Chawla *et al*, 2015; Zaibi *et al*, 2016). Although *P. aeruginosa* was the most common bacteria isolated in our study, it was found in only 13.2% of the total study subjects or 34.5% of those with a sputum culture positive for a potential pathogen, which is lower than that reported by previous studies (Araújo *et al*, 2018; Dhar *et al*, 2019). This may be because, many of our study subjects (73.6%) had no previous history of infection with their bronchiectasis and only a few (3.5%) had a destroyed lung on chest radiography, both previously reported as risk factors for *P. aeruginosa*

infection (Angrill *et al*, 2002; Chawla *et al*, 2015; Guan *et al*, 2014; Zaibi *et al*, 2016).

In our study, *P. aeruginosa* infection was more common among females, similar to the results of a study from Europe (Araújo *et al*, 2018). This might be a reason why females are reported to have more severe disease than males (Dimakou *et al*, 2016; Morrissey and Harper, 2004; Palwatwichai *et al*, 2002).

N-acetylcysteine is a mucolytic medication. N-acetylcysteine also has anti-inflammatory and antioxidant activity (Qi *et al*, 2019). A previous study from China reported long-term use of N-acetylcysteine may reduce the risk of infection in bronchiectasis patients (Qi *et al*, 2019). Spanish guidelines for the treatment of bronchiectasis include using N-acetylcysteine (Martínez-García *et al*, 2018). Some studies have reported N-acetylcysteine can inhibit biofilm formation and bacterial growth, while others report N-acetylcysteine increases bacterial biofilm formation and can decrease antibiotic activity *in vitro* (Hamilos, 2019; Landini *et al*, 2016; Rodríguez-Beltrán *et al*, 2015; Yin *et al*, 2018; Zhao and Liu, 2010). In our study, N-acetylcysteine use was associated with *P. aeruginosa* infection but only 21.5% of the subjects used N-acetylcysteine. A prospective randomized controlled trial with a larger population is needed to evaluate this association.

In our study, previous history of pulmonary tuberculosis was significantly associated with *P. aeruginosa* infection. Previously studies reported *P. aeruginosa* infection is more common in bronchiectasis and chronic obstructive pulmonary disease patients with a prior history of tuberculosis (Jin *et al*, 2018). Tuberculosis may cause architectural changes making it easier to get *P. aeruginosa* colonization and infection (Jin *et al*, 2018; Yum *et al*, 2014). Bronchiectasis patients with a prior history of pulmonary tuberculosis tend to have more episodes of infection and more severe disease; both of which have previously been reported as risk factor associated with *P. aeruginosa* infection (Dhar *et al*, 2019; Jin *et al*, 2018).

There were limitations to this study. We had a small study population. We also did not determine the association between smoking and poor lung function and *P. aeruginosa* infection since no *P. aeruginosa* infected subjects had spirometry tests and were current smokers. Another limitation of our study was the retrospective design that had no controls and no specifications on how and when sputum was collected. If the sputum was obtained after receiving antibiotic this might interfere with the culture results.

In our study of bacterial causes of lung infection among non-cystic fibrosis patients, potential pathogens were isolated in only 38% of the subjects. *P. aeruginosa* was the most common pathogen isolated. Female gender, prior history of pulmonary tuberculosis and N-acetylcysteine use were significantly associated with *P. aeruginosa* infection. Data from this study can inform initial empiric treatment of infection in non-cystic fibrosis bronchiectasis patients at the study hospital.

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