

PSEUDOMONAS AERUGINOSA IN HOSPITALIZED PATIENTS WITH INFECTIVE EXACERBATIONS OF BRONCHIECTASIS: CLINICAL AND RESEARCH IMPLICATIONS

Abdullah Al-Mobeireek, MRCP, FCCP; Abdul-Majeed Kambal, MRCPPath;
Saleh R. Al-Balla, FRCPC; Hassan Al-Sawwaf, MD; Sarfraz Saleemi, MRCP

Bronchiectasis is becoming less of a problem in developed countries since the advent of antibiotics and the implementation of immunization programs.^{1,2} It is still, however, a significant cause of illness in developing countries. To our knowledge, there are no statistics on the prevalence of bronchiectasis in Saudi Arabia. Nonetheless, many chest physicians would agree that patients with this disease are seen frequently, both in the outpatient and the inpatient settings.

Acute infective exacerbations related to bacterial pathogens are common and remain an important cause of morbidity and mortality in bronchiectasis. Even in the "stable" status between these exacerbations, it is believed that these organisms contribute to the perpetuation of the chronic inflammatory process and progressive lung damage. Identification and appropriate treatment of these pathogens is an essential part of the management.² The objective of this study was to determine the range and sensitivity of bacterial pathogens that are isolated from the respiratory secretions of patients admitted with infective exacerbations of bronchiectasis. Findings are compared with other studies, and the significance of bacterial isolates, particularly *Pseudomonas aeruginosa*, is discussed.

Patients and Methods

The study was conducted prospectively at King Khalid University Hospital (KKUH) and Sahary Chest Hospital in Riyadh, during the years 1994-1995. Both health institutions function as general and tertiary referral hospitals, serving the Central Province (Najd), but also at times accepting patients from other parts of the Kingdom.

All patients had bronchiectasis, defined by a history of

chronic productive cough and an abnormal permanent dilatation of one or more bronchi on plain film or computed tomography. These patients were admitted to one of the above hospitals through the emergency department on the basis of features that were compatible with infective exacerbations. For the purpose of this study, an infective exacerbation was defined as an increase in sputum quantity, or a change in the character of the sputum from mucoid to purulent. Patients were questioned about cough, sputum (quantity, color), hemoptysis, dyspnea, fever, the chronicity of these symptoms, any recent change, any preceding flu-like illness suggesting an upper respiratory tract infection (URTI), and the use of antibiotics within one month before admission. None of the patients had clinical features of cystic fibrosis (CF), and all patients under 20 years of age underwent sweat chloride tests.

Sputum samples were collected in sterile bottles and sent to the Microbiology Laboratory at KKUH and processed within one to two hours, or were kept at 4°C until processing. Gram staining was done by selecting a purulent portion of the specimen and spreading it on a microscopic slide with a sterile swab. Fields were examined to count the number of epithelial cells and neutrophils. Any specimen showing more than 25 epithelial cells per low-power field was considered unsuitable for further processing and another sample was requested from the ward. The most predominant bacteria was identified using 100x oil objective. For culturing, the specimens were homogenized by adding an equal volume of a mycolytic agent (sputolysin) and leaving them at room temperature for 15 minutes. The specimen was then cultured by placing one drop on a blood, a chocolate, a MacConkey and a Sabouraud agar plate. All plates were incubated at 37°C in 10% CO (carbon monoxide) atmosphere. The plates were read after 24 hours and the Sabouraud plates were reincubated for a further 24 hours if there was no growth. The bacterial isolates were identified using routine methods. The antibiotic susceptibility testing was performed using Stoke's method.

StatPac Gold statistical analysis package was used to find the significance by *t*-test.

From the Departments of Medicine (Drs. Al-Mobeireek, Al-Balla and Saleemi) and Microbiology (Dr. Kambal), King Khalid University Hospital and College of Medicine, King Saud University, and from the Sahary Chest Hospital (Dr. Al-Sawwaf), Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Al-Mobeireek: Department of Medicine (38), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11462, Saudi Arabia.

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TABLE 1. Clinical features associated with acute exacerbations in patients with bronchiectasis.

Clinical finding	Number of patients (n=100)
Increase in sputum quantity	100
Change in sputum color	100
Dyspnea	70
Fever	65
Clubbing	40
Hemoptysis	30
Cor pulmonale*	15
Recent upper respiratory tract infection	13

*As defined by WHO,¹⁸ right heart enlargement was assessed clinically by EKG and echocardiography.

TABLE 2. Results of sputum cultures in all groups and related to the etiology of bronchiectasis.

Organism growth	Post-TB (36)	Others (64)	All (100)
<i>Pseudomonas aeruginosa</i>	18	25	43
<i>Haemophilus influenzae</i>	4	6	10
<i>Streptococcus pneumoniae</i>	0	2	2
<i>Klebsiella</i> spp.	2	3	5
<i>Enterobacter cloacae</i>	1	0	1
<i>Acinetobacter</i> spp.	0	1	1
No growth	11	27	38

*The difference between the post-tuberculosis bronchiectasis and bronchiectasis related to other etiologies was not significant ($P>0.05$).

Results

One hundred patients were admitted throughout the study period, with infective exacerbation being the main reason for admission. Of these, 67 were females and 33 were males. The mean age was 60 (range 12 to 96) years. Causes of bronchiectasis were not definitely known in most cases (62%), although a post-infectious etiology was likely. Other causes included post-tuberculous (36%) and ciliary dyskinesia (2%). Prior use of antibiotics within one month before admission was reported by 37 patients (amoxicillin 36%, amoxicillin-clavulonic acid 28% and miscellaneous 36%). All patients reported an increase in sputum production, as well as a change in the color to cream, yellow or green. The mean hospital stay was five (range 1 to 28) days. Table 1 shows clinical features of the patients upon admission.

Sputum cultures were positive in 62 (62%). Table 2 shows the bacterial isolates. *Pseudomonas aeruginosa* (PA) was the most common organism (isolated in 43 patients), followed by *Haemophilus influenzae* (10) and *Klebsiella* spp. (5). *Streptococcus pneumoniae* was isolated in only two patients. Other gram-negative bacilli included *Enterobacter cloacae* (1) and *Acinetobacter* spp. (1). There was no significant difference in the type of pathogens between the post-tuberculous bronchiectasis and bronchiectasis related to other etiologies ($P>0.05$). PA was

sensitive to ceftazidime and ciprofloxacin, while 11% of PA were resistant to gentamicin.

Spirometry was available for 24 patients only (PA group 12, patients with other bacteria 12). Mean forced vital capacity (FVC) of the two groups were 59.8 ± 17.0 and 62.3 ± 17.4 of the predicted values, respectively. Mean forced expiratory volume in one second (FEV1) were 46.3 ± 18.3 and 53.8 ± 26.0 , respectively. The differences in these values between the two groups were not significant by the *t*-test ($P>0.05$).

Discussion

Pseudomonas aeruginosa was isolated in 43% of patients and compromised 72% of the identified bacterial pathogens from patients with infective exacerbations of bronchiectasis. A Medline search, as well as a search in the National Retrieval System (King Abdulaziz City for Science and Technology) did not yield any previous local studies for comparison. This finding is in contrast to earlier studies in the West, which showed that *Haemophilus influenzae* (HI) and *Streptococcus pneumoniae* were the most common organisms.^{3,4} However, in a recent study from the USA (that included 123 patients without a mention of the hospitalization or infection status), PA was the most common pathogen. PA was isolated in only 31% of patients, and formed 23% of isolated bacteria.⁵ In a Hong Kong study of 23 stable patients (without exacerbation), PA was also a major pathogen, but was superseded by HI.⁴ Patient populations may be different in these studies, and some were in stable condition without exacerbation. But all excluded patients with cystic fibrosis (CF), where the finding of PA is characteristic. It is unlikely that any of the patients in our series had CF. CF is a disease mainly of the white race, and usually presents during childhood, whereas the mean age in our group was 60 years. Very few reports of CF have come from Saudi Arabia, and have all been noted in children.⁶ Also, none of our patients had gastrointestinal disease, and all young patients underwent sweat chloride tests. It is apparent, therefore, that PA is becoming an important colonizer and pathogen in bronchiectasis related to other etiologies. Finally, as was found in a study in Japan,⁷ the post-tuberculous type has similar spectrum of organisms to the other types.

Cole proposed the "vicious circle" hypothesis, in which he attributed the perpetuation of the inflammatory process in bronchiectasis to the products resulting from the interaction of colonizing microorganisms and the leukocytes.⁸ PA in particular has been associated and implicated in the development of more severe forms of bronchiectasis, compared with other organisms.^{3,9-11} Animal and human studies have shown that PA produces a number of toxins, proteolytic enzymes and factors, such as exotoxin A, protease, elastases, leukocidin, phospholipase and others. These substances can cause epithelial

disruption, impairment of ciliary function and progressive airway damage, leading to bronchiectasis.^{3,11}

It is possible that the predominance of PA in this study was because patients came from tertiary care hospitals and were hospitalized, and thus may have more severe forms of bronchiectasis. Pulmonary function tests did not show a significant difference between the PA group and the others. Unfortunately, these tests were available for less than a quarter of the patients, and so this issue could not be resolved. Another reason could be the fact that many of the patients had been on wide spectrum antibiotics, with no effect on PA (37% within the month preceding admission), leading to the selective overgrowth of this organism.¹²

There are some clinical implications from this study. First, antibiotics are still considered a mainstay in the management of infective exacerbations of bronchiectasis.² It is believed that antibiotics reduce the bacterial load and, therefore, lessen the damage.^{13,14} In patients hospitalized with severe infection, PA should be considered a possible pathogen, and antibiotics coverage should, at least initially, include PA until information on culture and sensitivity is available. Strains of PA in this study were sensitive to ceftazidime and ciprofloxacin. In a study in Hong Kong,¹⁴ ofloxacin, a fluoroquinolone, was shown to be more effective than amoxicillin in treating infective episodes in bronchiectasis, again probably because of the predominance of PA.

Secondly, there are prognostic implications. Patients who harbor PA are likely to do worse in the long run. PA is associated with a more severe disease and a faster decline in lung function.³ Also, patients with unilateral disease who harbor PA have fewer chances of a cure after surgery, compared to those with other organisms.¹⁵ If other studies in our region confirm the predominance of PA, this would become a concern and would call for more attention and intense medical and physical therapy for those patients.

The study is limited by the fact that sputum only was used to identify the organisms, and this may have been liable to oropharyngeal contamination. It is noteworthy, however, that in CF the presence of *Pseudomonas* in the sputum was found to correlate well with bronchial secretions and lung tissue.^{16,17} The use of bronchial lavage and protected catheter would have been likely to give more accurate information, but not without risks in these patients who were acutely ill, with a compromised lung function. Thus, studies that used this technique, such as the Hong Kong study,⁵ were limited by a small number of patients who were in a stable clinical state.

In conclusion, this study shows the predominance of PA in the sputa of hospitalized patients with infective exacerbations of bronchiectasis. Such patients

probably have a less favorable prognosis and require more monitoring and intense general treatment, and in the case of infection, clinicians should consider PA as a possible pathogen. There were no resistant species in this study to ciprofloxacin or ceftazidime. We suggest further research in this region to include a wider range of patients with variable disease severity, assessment of physiological parameters (such as lung function and oxygenation), and methods that can avoid oropharyngeal contamination.

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