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Respiratory pathogens in patients with acute exacerbation of non-cystic fibrosis bronchiectasis from a developing country

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Authors' contributions: MI, study supervisor. All the authors made a substantive intellectual contribution, have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Abstract

Bronchiectasis unrelated to cystic fibrosis (non-CF bronchiectasis) has become a major respiratory disease in developing nations. The dilated mucus filled airways promote bacterial overgrowth

followed by chronic infection, bronchial inflammation, lung injury and re-infection Accurate pathogen identification and antimicrobial susceptibility allowing appropriate treatment, in turn, may break this vicious cycle. To study the spectrum and antimicrobial spectrum of pathogen yielded from respiratory specimens in adult patients with acute exacerbation of non-cystic fibrosis (CF) bronchiectasis. This cross-sectional study was performed at the pulmonology clinics of the Aga Khan University, Karachi, Pakistan from 2016-2019. Respiratory specimens were collected from adult patients with acute exacerbation of non-CF bronchiectasis presenting in pulmonology clinics. Microbial cultures were performed using standard methodology. Susceptibility testing was performed and interpreted using Clinical Laboratory Standard Institute criteria. A total of 345 positive cultures from 160 patients presenting with acute exacerbation were evaluated. The most frequent organisms were *Pseudomonas aeruginosa* (n=209) followed by *Hemophilus influenzae* (n=40) and *Staphylococcus aureus* (n=24). High rates of antimicrobial resistance were found in all these pathogens. Proportion of *Pseudomonas aeruginosa* strains resistant to ciprofloxacin, imipenem, ceftazidime and piperacillin-tazobactam were 27.1%, 16.8%, 14.8% and 13.1% respectively. 65% of *Hemophilus influenzae* strains were resistant to cotrimoxazole and ciprofloxacin and 66.7% of *Staphylococcus aureus* strains were resistant to methicillin. High antimicrobial resistance in non-CF bronchiectasis patients against commonly used antimicrobials is a concern and highlight need for urgent community level interventions to improve clinical outcome in these patients.

Key words: Bronchiectasis; etiology; infection; drug resistance.

Introduction

Bronchiectasis is a suppurative lung disease which is characterized by inflamed and dilated bronchi (1). Bronchiectasis unrelated to cystic fibrosis (non-CF bronchiectasis) has become a major primary respiratory disease in developing nations (2). It is a complex disease which gives rise to repeated chest infections due to a vicious cycle. The dilated airways filled with mucus promote growth of variety of organisms which is followed by chronic infection, bronchial inflammation, lung injury and re-infection (3). It is a cause of significant morbidity and mortality in adults and has multiple etiologies (e.g. autoimmune disease, cilia abnormalities, obstruction, infectious diseases, allergic bronchopulmonary aspergillosis (ABPA), connective tissue disease) and phenotypic features (4, 5). The mortality rate ranged from 10% to 16% over a 4-year observation period in a study conducted in USA, with culture positive for *Pseudomonas aeruginosa* in sputum, low BMI, male sex, advanced age and COPD identified as risk factors for mortality (4). Therefore, identifying the causative organism and its sensitivity may allow appropriate treatment, in turn, breaking the vicious cycle (3).

Gram negative bacteria are the most frequently seen organisms in the sputum of bronchiectasis patients (4). Studies conducted in adult populations of Spain, Greece, Thailand, Australia, UK and China identified *Haemophilus influenzae* and *Pseudomonas aeruginosa* as the most commonly isolated bacteria followed by *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Staphylococcus aureus* (1,5-11).

India conducted a first of its kind bronchiectasis study in a lower-middle income country in 2019 that showed *P. aeruginosa* to be the most common isolated pathogen followed by *Enterobacteriaceae*, *S. aureus, M. catarrhalis* and *H. influenzae* highlighting significant variation from Europe (12). A cohort study conducted in a tertiary care hospital in Karachi, Pakistan also reported *P. aeruginosa* as the most commonly cultured organism (36.2%) followed by *M. catarrhalis* and *H. influenzae* (13).

Exacerbations in non-CF bronchiectasis are a significant cause of morbidity (14). It has been hypothesized that the onset might be triggered by a change in airway bacterial composition, or spread of same species to new regions of the lung (15). Factors that contribute to pathogenesis of bronchiectasis can also cause exacerbations which include neurological disorders, poor nutrition, poverty etc. but it is assumed that a pathogen is always involved at some point (2).

P. aeruginosa has been seen to be the most common pathogen isolated in exacerbations (16,17) followed by *H. influenzae* (18), *S. pneumoniae, S. aureus, M. catarrhalis, Escherichia coli* and *Serratia* species in that order (14,15). A double-blind randomized control trial in New Zealand in 2012 also noted a similar trend with *H. influenzae* being the most common isolated pathogen (19). Sputum cultures from patients with bronchiectasis exacerbation, and on treatment in the ICU for acute respiratory failure, yielded *P. aeruginosa* most frequently followed by *S. pneumoniae* and *H. influenzae* (20).

In other studies conducted in Spain assessing the bacterial spectrum and antimicrobial resistance patterns in exacerbations, *P. aeruginosa* was noted to be the most common bacterial pathogen isolated, followed by *S. pneumoniae, H. influenzae, S. aureus* and Enterobacteriaceae (21,22). *P. aeruginosa* was also seen to be the most antibiotic resistant organism with isolates being ciprofloxacin resistant and multi-drug resistant (not susceptible to at least 1 agent in 3 or more antimicrobial classes) (21,22). Many of the *S. aureus* isolates were also found to be methicillin resistant (21,22).

Little has been published specifically on the spectrum and antibiotic resistance pattern of bacteria isolated from sputum cultures of adult patients with exacerbations of non-CF bronchiectasis from developing countries. Due to the rampant use of antibiotics, antimicrobial resistance is becoming a prominent concern for clinicians around the world, especially in developing countries. One of the main culprits for this situation is the ease with which antibiotics can be purchased over the counter, and an increased propensity of the clinicians for prescribing antibiotics. Data on spectrum of etiology, organisms and resistance in non-CF bronchiectasis is almost non-existent in the subcontinent and this study intends to bridge this gap. This study was conducted to identify the microbial agents present in sputum specimen and their resistance pattern in non-CF bronchiectasis patients with acute exacerbations.

Materials and Methods

This was a cross sectional study from the Aga Khan University Hospital (AKUH), Karachi, Pakistan (tertiary care hospital) over a 4-year period between 2016 and 2019. Adult patients (>18 years) diagnosed with non CF bronchiectasis on high resolution CT (HRCT) scan, who presented to outpatient pulmonology clinic with acute exacerbation, were included. Patients with a diagnosis of cystic fibrosis (CF) (or suspected CF) as well as patients who did not have HRCT scan were

excluded.An exacerbation of bronchiectasis was defined as a clinical diagnosis by the physician when the patient presented with one or more of the following symptoms: uncontrolled cough, increased sputum volume, worsened sputum purulence, aggravated dyspnea, fatigue, fever, and hemoptysis (23).

Clinical findings, etiology, microbiological culture of respiratory specimen samples and drug susceptibility was recorded on predesigned performa. All microbial cultures were conducted in the AKUH laboratory that is accredited with the College of American Physicians (CAP). All specimens were processed and reported using CAP standards. Susceptibility testing was performed and interpreted using Clinical Laboratory Standard Institute criteria. Sensitivity testing was carried out using the agar disc diffusion method. Vancomycin susceptibility testing was reported based on minimum inhibitory concentrations.

The study was approved by Ethical review committee (ERC) of Aga Khan University Hospital (ERC # (5097-MED-ERC-17, dated 27th November 2017).

The data was entered and analyzed using SPSS version 22.0. Baseline characteristics, etiology, frequency of isolation in cultures and resistance pattern of organisms were assessed and presented in percentages.

Results

A total of 160 patients who presented to AKUH pulmonology clinics with acute exacerbations of non-CF bronchiectasis and fulfilled the inclusion criteria were studied. Dimakou K, Triantafillidou C, Toumbis M, et al. Non CF-bronchiectasis: Aetiologic approach, clinical, radiological, microbiological and functional profile in 277 patients. Respir Med 2016;116:1-7.

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shows the demographic data of the studied population. Women (56.9%) and the age group >60 (46.9%) predominated.

Figure 1 summarizes the etiology of non-CF bronchiectasis in study population. The most common etiology seen was Post TB (n=65) which comprised of 40.6% of the sample followed by idiopathic (n=50) and ABPA (n=18).

A total of 345 positive respiratory specimen culture results from 160 patients, in the specified time duration, were evaluated. This equates to a mean of 2.2 sputum cultures per patient. A total of 20 different organisms were isolated from these patients (

Table *2*). The most frequently isolated organisms *were P. aeruginosa* from 209 samples (60.6%), *H. influenzae* from 40 patients (11.6%), *S. aureus* from 24 patients (7.0%), *Klebsiella pneumoniae* from 20 patients (5.8%), and *S. pneumoniae* from 19 patients (5.5%). Relatively rare organisms like Aeromonas species, Burkholderia cepacia, Chryseobacterium species, Nocardia species and Stenotrophomonas maltophilia were also seen. Twenty-seven (7.8%) cultures had a polymicrobial growth.

Figure 2 shows resistance patterns (including both resistant and intermediately resistant strains) of the four most frequently isolated organisms. *P. aeruginosa* isolates demonstrated highest resistance to aztreonam (32.0%) followed by ciprofloxacin (27.1%) and gentamicin (25.6%), while 44 (21%) of P. aeruginosa isolates were multi-drug resistant (not susceptible to at least 1 agent in 3 or more antimicrobial classes). *H. influenzae* isolates showed highest resistance to cotrimoxazole (65.0%) and ciprofloxacin (64.1%). *S. aureus* isolates were all resistant to penicillin (100%), followed by levofloxacin (83.3%), erythromycin (75%), gentamicin (50%), cotrimoxazole (29.2%), tetracycline (21.7%), clindamycin (20.8%) while 66.7% were categorized as MRSA. Vancomycin resistance was not observed. All of *K. pneumoniae* isolates were resistant to ampicillin, and 81.3% of isolates were resistant to cefuroxime followed by ciprofloxacin and cotrimoxazole. *S. pneumoniae* isolates were mostly sensitive to beta lactam but showed highest resistance to cotrimoxazole (72.2%) followed by tetracycline (52.9%) and erythromycin (50%).

Discussion

Our study demonstrated that the majority of the organisms isolated in the respiratory specimens in our patients population were gram negative (86%) concordant with the studies conducted in other parts of the world (4). *P. aeruginosa* was by far the most frequently isolated organism (60.6%) followed by *H. influenzae* (11.6%). Gram-positive organisms were less common with *S. aureus* and *S. pneumoniae* present in 7.0% and 5.5% of the samples respectively. These results are consistent with previous studies conducted on patients with bronchiectasis exacerbation (16,17,19,21-23). Additionally, a wide range of bacteria were isolated that included rare organisms like *Aeromonas species*, *Stenotrophomonas maltophilia* and *Chryseobacterium* species.

Clinical features, effect on lung function and disease severity vary with different bacteria. *P. aeruginosa* infections have been connected to worse pulmonary function, a greater spread of disease (extent of lung involvement), and poor quality of life (24,25). Patients, whose cultures

grow *P. aeruginosa* in acute exacerbation of bronchiectasis, are noted to have significantly higher number of hospital admissions in an year (20). This is coupled with a greater degree of bronchial wall thickening and dilatation, as well as greater degree of small airway disease (26). *P. aeruginosa* colonization has also been seen to be an independent predictor of mortality in bronchiectasis (27). This is alarming as a major portion of patients with exacerbation in our study cultured *P. aeruginosa*. This calls for infection control measures to be taken for prevention, as well as improved empirical and definitive treatment regimens (27). In addition, *H. influenzae* has been linked to significantly worsened CT scan findings (26).

P. aeruginosa strains had high resistance to aztreonam, ciprofloxacin and gentamicin. Ciprofloxacin resistance (27.1%) in our study was higher than has been observed in a previous study (18.4%) (21). 44 (21%) of the *P. aeruginosa* isolates (12.8% of all specimens) were multi-drug resistant (not susceptible to at least 1 agent in 3 or more antimicrobial classes). This is slightly higher than MDR *P. aeruginosa* isolates seen in previous studies in which MDR *P. aeruginosa* comprised of 7.9% and 6.6% of samples (21,22). Around two-thirds of the *S. aureus* isolates in our study were methicillin resistant which is twice as high as 25% and 35.3% seen in other studies (21,22). This difference in antibiotic resistance can be attributed to unrestricted supply of antibiotics in Pakistan (a developing/LMI country), excessive prescription due to patient demand, self-medication (28) for conditions that don't necessarily require antibiotics (flu, cough, abdominal pain, skin infections, fever etc.) (29), lack of basic knowledge about antibiotics (that includes correct dosage, indications *etc*.), illiteracy and failure to complete the antibiotic course after symptoms subside (30,31).

H. influenzae isolates showed high resistance to cotrimoxazole (65%) and ciprofloxacin (64.1%). *K. pneumoniae* isolates had high resistance to cefuroxime (81.3%) followed by ciprofloxacin and cotrimoxazole. *S. pneumoniae* isolates showed highest resistance to cotrimoxazole (72.2%) followed by tetracycline and erythromycin. Unfortunately, there is lack of data available to compare for resistance patterns of these organisms in bronchiectasis exacerbations throughout the world. In fact, to our knowledge, this is the first study to describe resistance pattern of all isolated organisms in bronchiectasis exacerbation. Antimicrobial resistance of these organisms has been studied in Pakistan for other respiratory infections including pneumonia, acute exacerbation of chronic bronchitis etc. *H. influenzae* isolates have been seen to exhibit lower rate of resistance to antimicrobials in the past with chloramphenicol and cotrimoxazole being notable exceptions

(32,33). *K. pneumoniae* has shown high resistance rates to ampicillin, cotrimoxazole and amoxicillin/clavulanic acid (34). High to moderate resistance to cotrimoxazole and erythromycin has been seen in *S. pneumoniae* isolates (32-35). *S. aureus* has been reported to be highly resistant to erythromycin and levofloxacin (34). These reported antimicrobial resistance patterns are consistent with the findings of our study.

Our study covers data from one tertiary care hospital in Pakistan. Since it is a private hospital, the patient population belongs to upper-middle class to upper class members of the society. Thus, it is not a true representation of the entire population of the city. Moreover, due to its reputation in the country, the pulmonology clinics receive relatively complicated cases and therefore the severity of disease studied may be different from that seen across the country. The study also covers a relatively small sample size of 160 patients.

Conclusions

P. aeruginosa was the most frequently isolated organism in the respiratory specimens of patients diagnosed with an acute exacerbation of non-cystic fibrosis bronchiectasis. 21% of the P. *aeruginosa* strains were multi-drug resistant. High resistance of *P. aeruginosa* strains to anti-pseudomonal antimicrobials was noted. This is a source of concern as it is the most frequently isolated organism and has been associated with poor prognosis in patients.

Since this study involves only one tertiary care hospital which caters to only one subset of the population, a multicenter country wide study with a larger sample size is needed to further evaluate the bacterial etiology and resistance pattern in the population of Pakistan.

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Table 1: Demographics of bronchiectasis patients.

Characteristics	Values	Range
Age (years)	*N (%)*	
18-30	25 (15.6%)	
31-45	32 (20%)	
46-60	28 (17.5%)	
>60	75 (46.9%)	
Age (mean ± SD)	54±19	18-101
Sex		
Female	91 (56.9%)	
Male	69 (43.1%)	
Female: Male Ratio	1.3:1	
BMI (mean ± SD)	22.03±6.63	14.6- 42.3
History of Influenza Vaccination	40 (25%)	
Rate of exacerbation /year (mean ± SD)	2.13±1.9	1- 5

Table 2: Bacterial species isolated from patients. The culture results were organized by organism cultured.

Organism	Frequency (n=345)	Percentage (%)
Pseudomonas aeruginosa	209	60.6
Hemophilus influenzae	40	11.6
Staphylococcus aureus	24	7.0
Klebsiella pneumoniae	20	5.8
Streptococcus pneumoniae	19	5.5
Acinetobacter species	12	3.5
Hemophilus parainfluenzae	12	3.5
Escherichia coli	11	3.2
Moraxella catarrhalis	6	1.7
Serratia species	3	0.9
Staphylococcus species (not aureus)	3	0.9
Enterococcus species	2	0.6
Nocardia asteroides	2	0.6
Pseudomonas species (not aeruginosa)	2	0.6
Stenotrophomonas maltophilia	2	0.6
Aeromonas species	1	0.3
Burkholderia cepacia	1	0.3
Chryseobacterium species	1	0.3
Enterobacter species	1	0.3

Figure 1: Etiology as defined at recruitment.

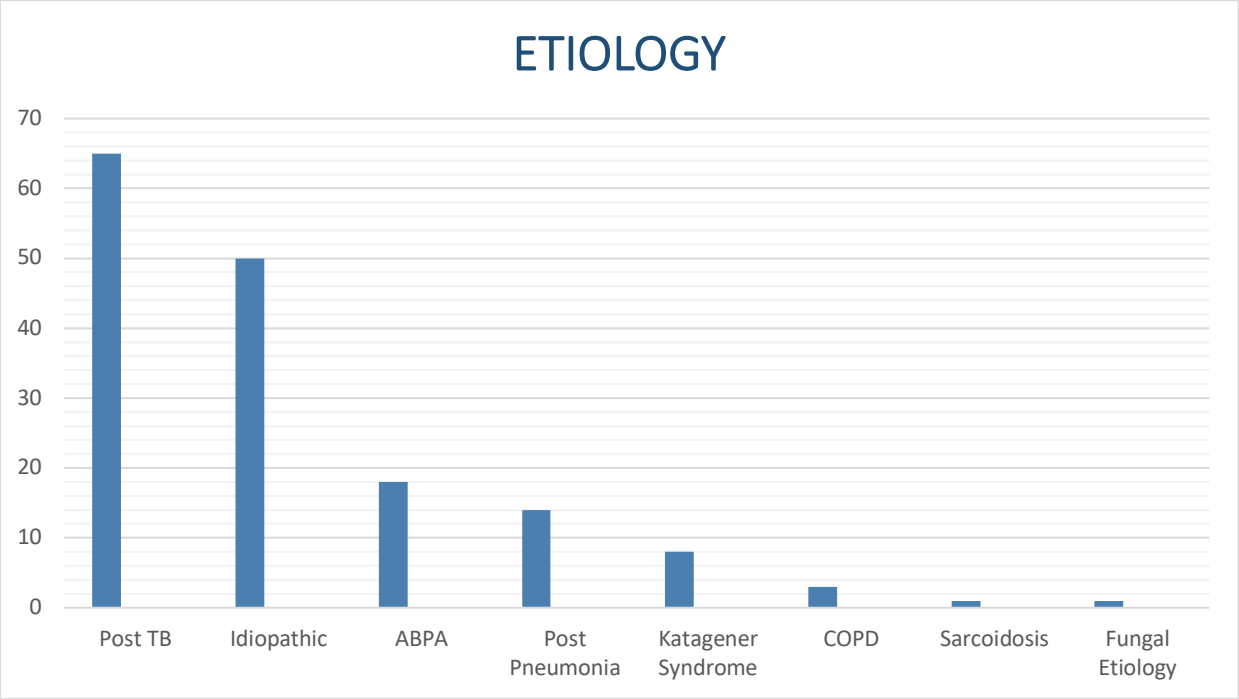

Figure 2: Antimicrobial resistance (% resistant isolates) in bacteria isolated from respiratory samples from non-CF bronchiectasis patients.