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Chronic Airway Infection and Resistance Pattern in Children and Adults with Cystic Fibrosis in Oman: A Single-center Cross-section Study

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Abstract

Background: Cystic fibrosis (CF) is a multisystemic genetic disease. Progressive decline in lung function is the major cause of morbidity and mortality in this population. This is primarily related to chronic airway infection and recurrent pulmonary exacerbations. Our objective is to assess the pattern of airway bacterial growth among CF patients in Oman and to identify possible risk factors for the hypothesized early *Pseudomonas Aeruginosa (PA)* acquisition among these children.

Methods: This is a retrospective single-center cross-sectional study that included all patients who attended the CF clinic between 2004 and 2020. Data included age, sex, geographic region, date of CF diagnosis, CF genotype, number of siblings with CF, and date and results of all positive respiratory cultures. Early PA was defined by a positive respiratory culture for *PA* before the age of two years. *Multi-drug resistant PA (MDRO)* was defined as PA that is not susceptible to ≥1 agent in ≥ 3 classes of antimicrobials. The above factors were compared between the two groups of early and late *PA* acquisition.

Results: A total number of 114 patients were included, and a total of 2393 positive bacterial cultures were studied. Eighty-four patients (73.6%) were identified to have a positive culture with PA, including 40 (47.6%) who acquired it before the age of 2 years. *PA* remained the most common organism across all age groups. Twenty-six patients (22.8%) were positive for *PA* on their first respiratory culture while 56 patients (49.1%) had three or more positive respiratory cultures for *PA. MRSA* accounted for 7.2% of all positive cultures below the age of 1 year and peaked at 14.8% between the ages of 4 and 5 years. There was a significant relationship between early *PA* acquisition and male sex. No significant relationship was seen between CF genotype, geographic region, age at diagnosis, or the presence of a sibling with CF and early acquisition of *PA.*

Conclusions: In contrast to international data, our study showed earlier acquisition of *PA* and its predominance among children with CF in Oman. Male sex carried a higher risk for early PA acquisition. Further prospective studies are needed to confirm this relationship and identify other possible risk factors. These results will impact the clinical practice of CF physicians in Oman.

Keywords: Cystic fibrosis, Pseudomonas Aeruginosa, Chronic airway infection, Pseudomonas Aeruginosa eradication

Introduction

Cystic Fibrosis (CF) is one of the most common autosomal recessive diseases, affecting around 1 in every 2000 live births. CF is more frequently seen among the Caucasian and Northern European descent populations.[1] The estimated prevalence of CF in Oman is 10.3 per 100,000 individuals. The commonest genotypes in Oman are p.Ser549Arg and DelF508, with a prevalence of 51.9% and 12.3%, respectively.[2]

CF is a multisystemic disease that affects more than one organ. Progressive decline in lung function is the major cause of morbidity and mortality in this population.[3] This decline in lung function is related to chronic airway infection and recurrent pulmonary exacerbations.[4,5] The microorganism causing this chronic infection and its resistance pattern play a major role in the trajectory of lung function decline in this population.[6,7] Routine sampling to obtain respiratory cultures at every clinic visit -even in the absence of respiratory symptoms- and during CF exacerbations is recommended. Sputum is the preferred method. However, in patients who cannot expectorate such as young children, cough or throat swabs and oropharyngeal suction are acceptable alternatives and have been shown to correlate with lower airway sampling in CF. This routine surveillance can guide proactive eradication for certain bacteria like *Pseudomonas aeruginosa (PA),* the antibiotic choice during exacerbation, and helps in infection control measures.[8]

PA is a common pathogen in CF, and it has been shown to result in a shortened life expectancy in this population.[9] In our region, it has been noted that CF patients tend to get earlier growth of *PA* from respiratory cultures compared to the international data. A study conducted in Saudi Arabia showed that *PA* was the most common organism in first-taken culture from CF children (44%), followed by *H. Influenza* (16%) and *Methicillin-Susceptible Staphylococcus Aureus (MSSA)* (15%).[10] Several risk factors have been reported in the literature for early *PA* acquisition, including female gender, CFTR genotype, and coinfection with *MSSA*.[11,12] A recent study showed that a previous infection with any bacterial pathogen increases the risk of PA acquisition with a 16% increase for every additional pathogen.[13]

Methicillin-resistant Staphylococcus Aureus (MRSA) is another emerging challenge for patients with CF, which is associated with worse survival.[14] Several risk factors of persistent *MRSA* have been identified, including pancreatic insufficiency status, CF-related diabetes, hospitalization rate, co-infection with *PA* and being cared for in a center with a higher prevalence of *MRSA* infection.[15]

To our knowledge, no study in Oman investigated the microbiological pattern of chronic airway infections in CF patients. This study aimed to assess the pattern of airway bacterial growth among CF patients at different age groups in Oman. It also aims to identify possible risk factors for the hypothesized early *PA* acquisition among our CF patients. This would guide CF healthcare providers in Oman in their preventive and treatment strategies. It may also open the door for further prospective and environmental studies to identify modifiable risk factors for early *PA* infection.

Methods

This is a retrospective single-center cross-sectional study that was approved by the Ministry of Health Centre of Studies and Research (Ethical approval Number SRC#67/2020). The study included all patients who attended the CF clinic in the period between 2004 and 2020 at the Royal Hospital, Oman, which is one out of two CF centers in the country. The 16-year period was chosen based on the availability of electronic data records.

The diagnosis of CF in this study followed the international criteria which requires the presence of at least one of the typical phenotypic features, e.g., chronic pulmonary disease, chronic sinusitis, characteristic gastrointestinal and nutritional abnormalities, and salt loss syndromes or a history of CF in a sibling or a positive newborn screening test, along with either one of the following: a positive sweat chloride test, a two CFTR mutation known to cause CF on separate alleles or an abnormality in Nasal Potential Difference (NPD) testing.[16]

Data were retrieved from the electronic health records (Al-Shifa system), which included demographic information, i.e., (current age, sex, date of birth and geographic region), date of CF diagnosis, genotype and number of siblings diagnosed with CF. The dates and results of all respiratory cultures including cough swabs, nasopharyngeal aspirate, bronchoalveolar lavage (BAL) and sputum cultures were obtained to capture all airway sampling methods used by the treating team. In addition, dates of hospitalizations secondary to CF exacerbation and the antibiotics used during these admissions were collected. Age at first acquisition of different microorganisms was calculated from date of brith and date of positive culture. *Multi-drug resistant PA (MDRO) is* defined as PA that is not susceptible to ≥1 agent in ≥ 3 classes of antimicrobials. For *PA*, the participants were divided into two groups based on the age of the first *PA*-positive culture. Early acquisition of *PA* was defined as the first positive culture of PA before the age of two years, and the two groups, i.e., early and late acquisition, were compared in terms of gender, CFTR mutation, geographic area, and having a sibling with CF. The data were analyzed using the Statistical Package for Social Sciences (SPSS). Categorical variables were described using frequency and percentages. The relation between the variables was analyzed using Chi-Square test, and T-test. The Mann-Whitney U test was used for pairwise comparisons between two independent groups, while the Kruskal-Wallis test was employed to assess differences among three or more independent groups. A p-value of < 0.05 was considered statistically significant.

Results

Baseline demographics are shown in Table 1. The study included 114 patients, 60.5% were male. The majority of patients were homozygous p.Ser549Arg (60.5%) and most commonly from the North Al Batinah region (45.6%).

Table 1: Patients' demographics.

		Absolute number / %
Gender	Male	69 (60.5%)
	Female	45 (39.4%)
Region of Oman	Al Dhakiliah	20 (17.5%)
	North Al Batinah	52 (45.6%)
	Al Dhahira	15 (13.2%)
	Al Buraimi	5 (4.4%)
	South Al Batina	15 (13.2%)
	Muscat	5 (4.4%)
	South Al Sharqiya	1 (0.9%)
	Dhofar	1 (0.9%)
Siblings with Cystic Fibrosis	No siblings	68 (59.6%)
	≥1 siblings	46 (40.3%)
CFTR Genotypes*	Homozygous p.Ser549Arg	69 (60.5%)
	Homozygous DelF508	12 (10.5%)
	Other heterozygous	16 (14.0%)
	Other homozygous	11 (9.6%)

** Cystic fibrosis transmembrane conductance regulator (CFTR) genotype is missing for six patients*

A total of 2393 positive bacterial cultures were studied. The sampling methods were either sputum culture (1533 = 66.6%) or cough swab culture (768 = 33.4%). From all positive bacterial cultures, *PA* accounted for 713 cultures (43.3%), followed by *MSSA* (15%) and *H. influenza* / *Parainfluenza* (8.5%). *MRSA* accounted for 5.7% of positive cultures, while *Multi-Drug Resistant PA (MDRO)* accounted for 3.7%. *Klebsiella pneumonia* and *Stenotrophomonas maltophilia* accounted for 3.1% and 1.3% of cultures, respectively. *PA* is the most common organism among all age

groups, accounting for 30.4% of all respiratory cultures obtained before the age of 1 year which peaks up to 58.2% between 2 and 3 years of age. Half of the studied population were *PA* positive by 29 months of age. Twenty-six patients (22.8%) were positive for *PA* on their first respiratory culture while 56 patients (49.1%) had three or more positive respiratory cultures for *PA. MRSA* accounted for 7.2% of all positive cultures below the age of 1 year and peaked at 14.8% between the ages of 4 and 5 years (Figure 1).

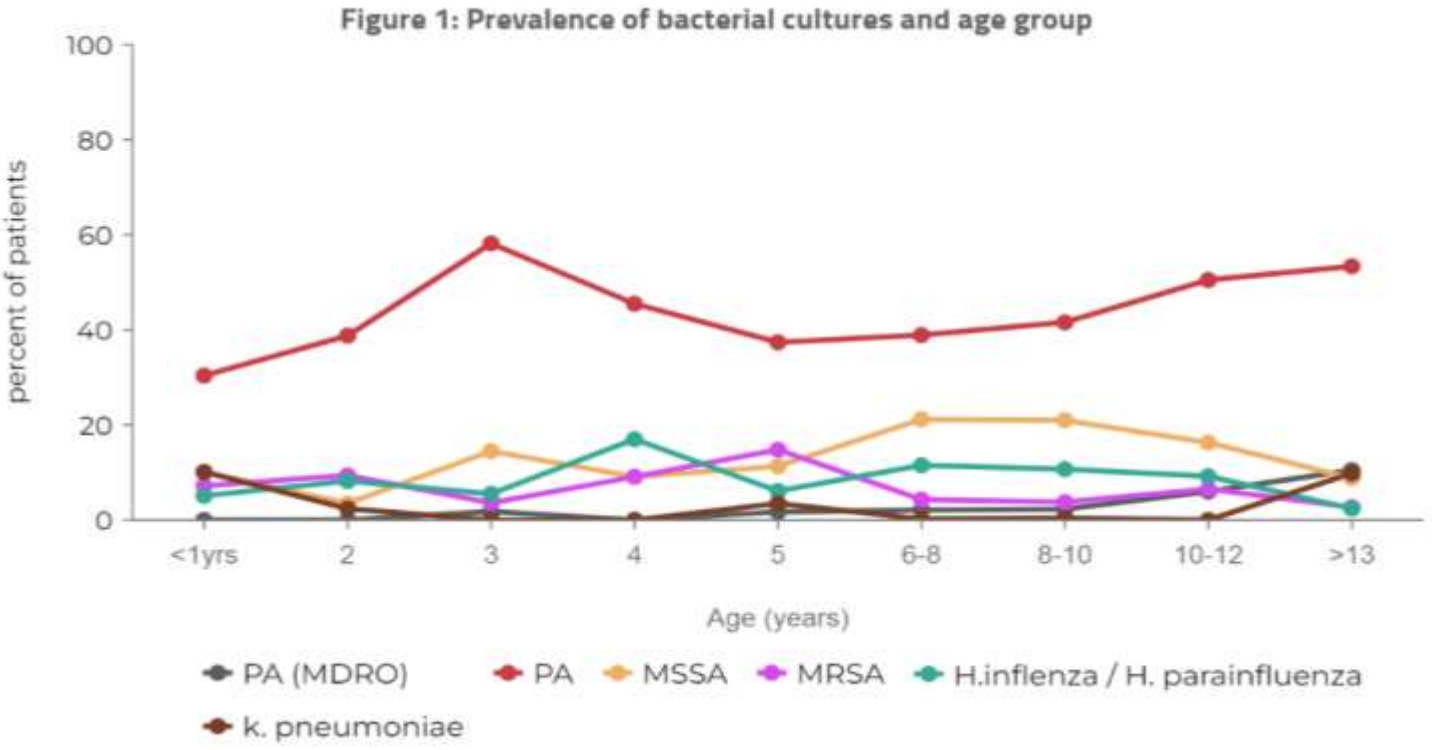

Figure 1: Prevalence of bacterial Culture distributed based on age group. PA = Pseudomonas aeruginosa, PA (MDRO) = Multi drug resistance Pseudomonas aeruginosa, MSSA= Methicillin-resistant Staphylococcus aureus, MRSA = Methicillin-resistant Staphylococcus aureus.

Patients were divided based on their age at the first *PA* acquisition into two groups for comparison: less than or equal to 24 months and more than 24 months of age. Of all studied patients, 40 patients (47.6%) had early *PA* infection, and 44 (53.4%) had a late infection.

The hypothesized risk factors for early *PA* acquisition, including sex, the geographic region of Oman where the patient is coming from, CF genotype, and the presence of one or more siblings with CF, were studied. Male sex showed a statistically significant relationship, in which male patients had earlier *PA* acquisition. None of the other risk factors showed a statistically significant relationship with early *PA* acquisition (Table 2).

Table 2: Risk factors compared between early Pseudomonas Aeruginosa (PA) acquisition (defined by a positive respiratory culture for PA before the age of two years) and late acquisition groups.

Risk factors	Early PA	Late PA	p Value
Number (%)	40 (47.6%)	44 (52.4%)	

Gender	Male	29 (74.4%)	23 (52.3%)	**0.03**
	Female	10 (25.6%)	21 (47.7%)	
Region	Al Dhakiliah	7 (7.5%)	8 (18.2%)	0.41
	North Al Batinah	18 (45%)	21 (47.7%)	
	Al Dhahira	8 (20%)	3 (6.8%)	
	Al Buraimi	2 (5.0%)	1 (2.3%)	
	South Al Batina	4 (10%)	9 (20.5%)	
	Muscat	1 (2.5%)	2 (4.5%)	
Siblings	No siblings with CF	24 (60%)	29 (65.9%)	0.57
	One or more siblings with CF	16 (40%)	15 (34.1%)	
CFTR Genotypes*	Homozygous p.Ser549Arg	26 (65%)	32 (76.2%)	0.41
	Homozygous DelF508	4 (10%)	5 (11.9%)	
	Other heterozygous	4 (10%)	1 (2.4%)	
	Other homozygous	6 (15%)	4 (9.5%)	

** Cystic fibrosis transmembrane conductance regulator (CFTR) genotype is missing for two patients in the late PA group*

Discussion

Our study showed that CF patients in Oman acquire PA at an early age. It also showed that PA is the most common organism isolated from respiratory cultures obtained from CF patients across all age groups. This is in contrast to the international data. For example, according to the Cystic Fibrosis Foundation Patient Registry (CFFPR) 2021 report, *MSSA* was the most common organism among all pediatric age groups.[17] Australian cystic fibrosis date registry (ACFDR) showed a similar predominance of *MSSA* in children less than 7 years of age (22%), followed by *H.Influnzae* (20%).[18] A study done in Spain showed that *MSSA* was the most common infection in young patients between the ages of 6-10 years, while *PA* infections started to be more prevalent around the late adolescent age group.[19] Another study from the US showed that *H.Influenzae* was the most prevalent organism that grew from respiratory cultures obtained from children less than 2 years of age.[20] Of note, a population-based study in the US showed that the overall incidence of *PA* was less in 2020 (36%) compared to 2018 (51%), which suggested a trend towards a decline in PA infection.[7] While our results differ from the international data, they resemble the data reported from our region. A study from Saudi Arabia showed that CF patients tend to have early *PA* infection and that *PA* was the most prevalent bacterial culture among CF patients.[10] Another follow-up study done in Saudi Arabia showed that there was an increase in the prevalence of *PA* from 34% to 53% and a decrease in the prevalence of *MSSA* and *H. influenza* during their 7-year follow-up period.[21]

PA (MDRO) defined as *PA* that is not susceptible to ≥1 agent in ≥ 3 classes of antimicrobials is an emergent challenge among the CF population. In our study, it was more prevalent in patients older than 13 years of age (10.5%). Also, in our study, among all positive cultures, *PA (MDRO)* accounted for (3.7%) which was almost similar to the CFFPR-2021 report, which showed that among all cultures of CF patients in 2021, (3.5%) reported having *PA (MDRO)*.[17]

In addition, in our study, *MRSA* peaked at the age of 5 years (14.8%), whereas, in the CFFPR-2021 report, the highest prevalence of *MRSA* occurs in individuals between the ages of 10 and 20, accounting for about (20%) of the positive cultures.[17] Similarly, regional data from Saudi Arabia showed a prevalence of 11% among their CF patients which was acquired at a mean age of 10.4 ± 7.2 years. This study also noted an increasing trend of MRSA infection as 79% of positive cultures were in the period between 2010 to 2016 compared to 26% in the period between 2002 and 2009.[22]

Several risk factors for early *PA* acquisition were reported in the literature. A study in the USA by Maselli JH et al. showed an association between female sex, homozygous deltaF508 mutation, co-infection with *MSSA*, and early *PA* acquisition. The same study showed that there is a possible association between length of stay in hospital and early colonization with *PA*.[23] In our study, male patients had earlier *PA* acquisition. There was no statistically significant difference in CFTR genotype between the early and late PA groups.

In a study looking into the possibility of social interaction as a risk factor for early *PA* infection, the interaction of a younger patient with an older CF patient was found to be a risk factor.[16] Other studies showed that CF siblings can have *PA* cross-infection.[24,25] In our study, the presence of a sibling with CF was not a statistically significant risk factor for early acquisition of *PA*.

Few environmental factors have been studied previously to address the causes of *PA* infections. The Morbidity and Mortality Weekly Report (MMWR) of the Centers for Disease Control and Prevention (CDC) surveillance for waterborne disease outbreaks in the US (1993-1994) showed that water sources like hot tubs and swimming pools are sources for *PA* infections.[26] Another study showed that jacuzzies and hot tubs had the highest sources of *PA* infections among the studied water sources.[27] These parameters could not be studied in our study, but there was no relationship between demographic region and early acquisition of *PA*.

In an adult study, it was noted that in Chronic Obstructive Pulmonary Disease (COPD) patients, pathogenic bacteria were isolated from the nebulization sets, which includes *PA* along with other pathogens.[28] This is a possible risk factor in our population, but it was not possible to retrieve this data given the retrospective nature of our study.

Several limitations can be highlighted in this study. Being a retrospective study, the risk of missing data is present. The difference in airway sampling methods, e.g., sputum culture, BAL, or cough and throat swab, was not controlled. Some of the possible risk factors, such as healthcare facility visits prior to diagnosis or water contamination, could not be studied. Based on that, we recommend future prospective studies in Oman addressing the above limitations. These studies should focus on healthcare exposures before CF diagnosis including receiving nebulized medications, co-infection within the same institution, and environmental surveillance.

Conclusion

Our data showed an early acquisition of *PA* and its predominance across all age groups. Among the studied risk factors, only the male sex showed a significant relationship with early *PA* acquisition. Early lower airway sampling with BAL for early *PA* detection and eradication could be considered by CF healthcare providers. Further studies are needed to investigate the environmental risk factors for early *PA* acquisition in Oman.

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Disclosure

There is no conflict of interest to be disclosed, all articles used for literature review are available for everyone.

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