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

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ABSTRACT

Objectives: Cystic fibrosis (CF) is a multisystemic genetic disease. Progressive decline in lung function is the major cause of morbidity and mortality in this population, primarily related to chronic airway infection and recurrent pulmonary exacerbations. We sought to assess the pattern of airway bacterial growth among patients with CF in Oman and identify possible risk factors for the hypothesized early *Pseudomonas aeruginosa* acquisition among this population. ***Methods***: We conducted a retrospective single-center cross-sectional study that included all patients who attended the CF clinic at Royal Hospital, Oman between 2004 and 2020. Collected data included age, sex, geographic region, date of CF diagnosis, CF genotype, number of siblings with CF, and the date and results of all positive respiratory cultures. Early *P. aeruginosa* acquisition was defined by a positive respiratory culture for *P. aeruginosa* before the age of two years. Multi-drug resistant *P. aeruginosa* was defined as *P. aeruginosa* not susceptible to ≥ 1 agent in ≥ 3 classes of antimicrobials. The above factors were compared between the early and late *P. aeruginosa* acquisition groups. ***Results:*** A total of 114 patients were included, and 2393 positive bacterial cultures were analyzed. Eighty-four (73.7%) patients were identified to have a positive culture for *P. aeruginosa*, including 40 (47.6%) who acquired it before the age of two years. *P. aeruginosa* remained the most common organism across all age groups. Twenty-six (22.8%) patients were positive for *P. aeruginosa* on their first respiratory culture, while 56 (49.1%) patients had three or more positive respiratory cultures for *P. aeruginosa*. Methicillin-resistant *Staphylococcus aureus* accounted for 7.2% of all positive cultures under the age of one year and peaked at 14.8% between the ages of four and five years. A significant association were found between early *P. aeruginosa* acquisition and male sex. No significant association was observed between CF genotype, geographic region, age at diagnosis, or the presence of a sibling with CF and early *P. aeruginosa* acquisition. ***Conclusions:*** Our study demonstrated earlier acquisition of *P. aeruginosa* and its predominance among children with CF in Oman. Male sex was associated with a higher risk for early *P. aeruginosa* acquisition. Further prospective studies are needed to confirm this association and identify other possible risk factors. These findings will impact the clinical practice of CF physicians in Oman.

Cystic fibrosis (CF) is one of the most common autosomal recessive disorders, affecting approximately 1 in every 2000 live births. It is more frequently observed among the Caucasian and Northern European descent populations.[1] In Oman, the estimated prevalence of CF is 10.3 per 100 000 individuals. The most common transmembrane conductance regulator (CFTR) genotypes in Oman are p.Ser549Arg and DelF508, with prevalences of 51.9% and 12.3%, respectively.[2]

CF is a multisystemic disease that affects multiple organs. Progressive decline in lung function is the primary cause of morbidity and mortality in this population.[3] This decline is related to chronic airway infection and recurrent pulmonary exacerbations.[4,5] The microorganism causing this chronic infection and its resistance pattern play a significant role in

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the trajectory of lung function decline.[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 are unable to 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,* the antibiotic choice during exacerbation, and helps in infection control measures.[8]

P. aeruginosa is a common pathogen in CF and has been associated with reduced life expectancy in this population.[9] In the Middle East, it has been noted that CF patients tend to get earlier growth of *P. aeruginosa* from respiratory cultures compared to international data. A study conducted in Saudi Arabia found that *P. aeruginosa* was the most common organism in first-taken culture from CF children (44%), followed by *Haemophilus influenza* (16%) and Methicillin-Susceptible *Staphylococcus aureus* (MSSA) (15%).[10] Several risk factors for early *P. aeruginosa* acquisition have been reported in the literature, including female sex, CFTR genotype, and coinfection with MSSA.[11,12] A recent study showed that a prior infection with any bacterial pathogen increases the risk of *P. aeruginosa* acquisition with a 16% increase for every additional pathogen.[13]

Methicillin-resistant *S. aureus* (MRSA) is another emerging challenge for patients with CF, which is associated with reduced survival.[14] Several risk factors for persistent MRSA have been identified, including pancreatic insufficiency status, CF-related diabetes, hospitalization rate, co-infection with *P. aeruginosa,* and receiving care at a center with a higher prevalence of MRSA infection.[15]

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

METHODS

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

In this study, the diagnosis of CF was based on international criteria, which requires the presence of at least one typical phenotypic feature (e.g., chronic pulmonary disease, chronic sinusitis, characteristic gastrointestinal and nutritional abnormalities, salt loss syndrome), a history of CF in a sibling, or a positive newborn screening test along with one of the following: a positive sweat chloride test, two CFTR mutation known to cause CF on separate alleles, or an abnormality in nasal potential difference testing.[16]

Demographic information (including current age, sex, date of birth, and geographic region), date of CF diagnosis, genotype, and number of siblings diagnosed with CF were retrieved from the electronic health records (Al-Shifa system). The dates and results of all respiratory cultures, including cough swabs, nasopharyngeal aspirate, bronchoalveolar lavage, and sputum cultures, were obtained to capture all airway sampling methods used by the treating team. Additionally, hospitalizations dates related to CF exacerbation and the antibiotics used during these admissions were collected. Age at first acquisition of different microorganisms was calculated from date of birth and date of positive culture. Multi-drug resistant *P. aeruginosa* (MDRO) is defined as *P. aeruginosa* not susceptible to ≥ 1 agent in ≥ 3 classes of antimicrobials. Participants were divided into two groups based on the age of the first *P. aeruginosa* positive culture: early acquisition, defined as the first positive culture of *P. aeruginosa* before the age of two years, and the late acquisition. The two groups were compared in terms of sex, CFTR mutation, geographic area, and presence of a sibling with CF.

The data were analyzed using SPSS Statistics (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp.). Categorical variables were described using frequencies and percentages. Relationships between the parametric variables were analyzed using the chi-square test and *t*-test, while non-

parametric variables were assessed using the Mann-Whitney U test for pairwise comparisons between two independent groups and the Kruskal-Wallis test to evaluate differences among three or more independent groups. A *p*-value of < 0.05 was considered statistically significant.

Table 1: Patients' demographics.

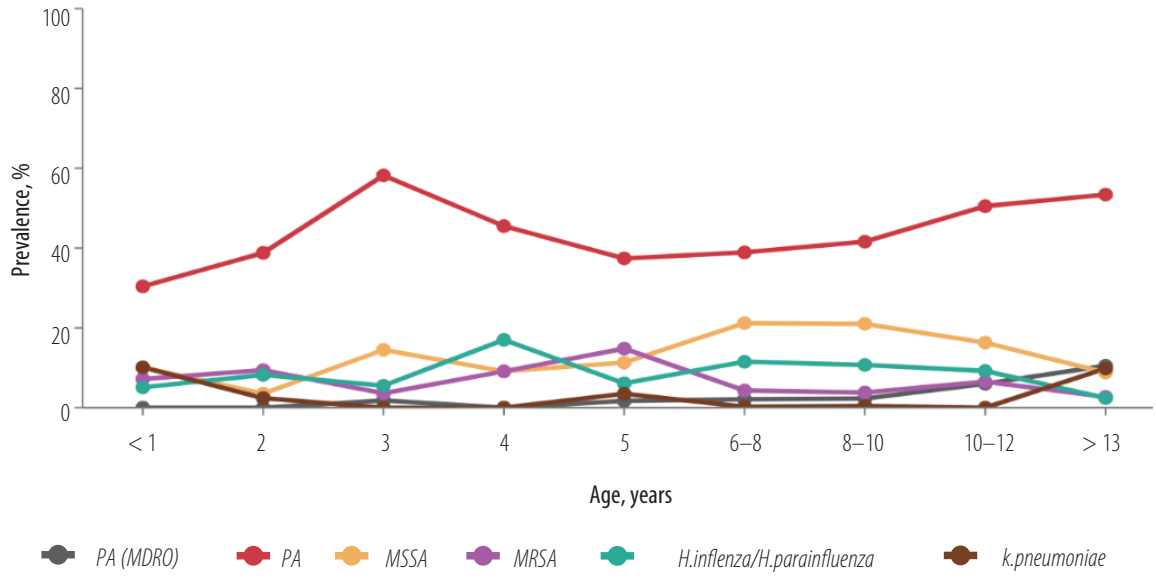
Variables	n (%)
Sex	
Male	69 (60.5)
Female	45 (39.5)
Governorate	
Al Dhakiliah	20 (17.5)
North Al Batinah	52 (45.6)
Al Dhahira	15 (13.2)
Al Buraimi	5 (4.4)
South Al Batinah	15 (13.2)
Muscat	5 (4.4)
South A'Sharqiyah	1 (0.9)
Dhofar	1 (0.9)
Siblings with cystic fibrosis	
0	68 (59.6)
≥ 1	46 (40.4)
CFTR 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.*

RESULTS

The study included 114 patients, with 60.5% being male. The majority of patients were homozygous p.Ser549Arg (60.5%) and most commonly originated from the North Al Batinah governorate (45.6%) [Table 1].

A total of 2393 positive bacterial cultures were studied. Sampling methods included sputum (n = 1533, 66.6%) and cough swab culture (n = 768, 33.4%). Among all positive bacterial cultures, *P. aeruginosa* 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 MDR *P. aeruginosa* accounted for 3.7%. *Klebsiella pneumonia* and *Stenotrophomonas maltophilia* accounted for 3.1% and 1.3% of cultures, respectively. *P. aeruginosa* was the most common organism across all age groups, accounting for 30.4% of all respiratory cultures obtained before the age of one year, which peaked up to 58.2% between two and three years of age. Half of the studied population were *P. aeruginosa* positive by 29 months of age. Twenty-six (22.8%) patients were positive for *P. aeruginosa* on their first respiratory culture, while 56 (49.1%) patients had three or more positive respiratory



PA: Pseudomonas aeruginosa; PA (MDRO): multi-drug resistance P. aeruginosa; MSSA: methicillin-sensitive Staphylococcus aureus; MRSA: methicillin-resistant S. aureus.

Figure 1: Prevalence of bacterial culture distributed based on age group.

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

Risk factors	Early acquisition n (%)	Late acquisition n (%)	*p*-value
Number (%)	40 (47.6)	44 (52.4)	
Sex			
Male	29 (72.5)	23 (52.3)	0.03
Female	11 (27.5)	21 (47.7)	
Governorate			
A'Dakhiliah	7 (17.5)	8 (18.2)	0.41
North Al Batinah	18 (45.0)	21 (47.7)	
A'Dhahirah	8 (20.0)	3 (6.8)	
Al Buraimi	2 (5.0)	1 (2.3)	
South Al Batinah	4 (10.0)	9 (20.5)	
Muscat	1 (2.5)	2 (4.5)	
Siblings with cystic fibrosis			
0	24 (60.0)	29 (65.9)	0.57
≥ 1	16 (40.0)	15 (34.1)	
CFTR genotypes*			
Homozygous p.Ser549Arg	26 (65.0)	32 (76.2)	0.41
Homozygous DelF508	4 (10.0)	5 (11.9)	
Other heterozygous	4 (10.0)	1 (2.4)	
Other homozygous	6 (15.0)	4 (9.5)	

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

cultures for *P. aeruginosa.* MRSA accounted for 7.2% of all positive cultures under the age of one year and peaked at 14.8% between the ages of four and five years [Figure 1].

Patients were divided into two groups based on the age at which they first acquired *P. aeruginosa*: ≤ 24 months (early acquisition) and > 24 months old (late acquisition). Of all studied patients, 40 (47.6%) had early *P. aeruginosa* acquisition, while 44 (53.4%) had a late acquisition.

The hypothesized risk factors for early *P. aeruginosa* acquisition, including sex, governerate where the patient came from, CF genotype, and the presence of one or more siblings with CF, were studied. Male sex showed a statistically significant association with earlier *P. aeruginosa* acquisition. None of the other risk factors showed a statistically significant association with early *P. aeruginosa* acquisition [Table 2].

DISCUSSION

Our study demonstrated that patients with CF in Oman acquire *P. aeruginosa* at an early age. It also showed that *P. aeruginosa* is the most common organism isolated from respiratory cultures across all age groups in CF patients. This contrasts with the international data. According to the 2021 Cystic Fibrosis Foundation Patient Registry (CFFPR) report, MSSA was the most common organism among all pediatric age groups.[17] Similarly, the Australian Cystic Fibrosis Data Registry showed a predominance of MSSA in children under seven years of age (22%), followed by *H. influenzae* (20%).[18] A study conducted in Spain showed that MSSA was the most common infection in young patients between the ages of 6–10 years, while *P. aeruginosa* infections became more prevalent in the late adolescent age group.[19] Another study from the US reported that *H. influenzae* was the most prevalent organism to grow from respiratory cultures in children under two years old.[20] Additionally, a population-based study in the US showed that the overall incidence of *P. aeruginosa* was lower in 2020 (36%) compared to 2018 (51%), suggesting a declining trend.[7] While our findings differ from the international data, they are consistent with data from the region. A study from Saudi Arabia showed that CF patients tend to have early *P. aeruginosa* infection and it was the most

prevalent bacterial culture.[10] Another follow-up study conducted in Saudi Arabia revealed an increase in the prevalence of *P. aeruginosa* from 34% to 53% and a decrease in the prevalence of MSSA and *H. influenza* over a seven-year period.[21]

MDR *P. aeruginosa*, defined as *P. aeruginosa* 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 ≥ 13 years (10.5%). Among all positive cultures, MDR *P. aeruginosa* accounted for 3.7%, which is comparable to the 3.5% reported in the CFFPR-2021.[17]

We observed a peak of MRSA at five years old (14.8%). In contrast, the CFFPR-2021 report showed the highest prevalence of MRSA in individuals aged 10–20 years, accounting for approximately 20% of positive cultures.[17] Similarly, regional data from Saudi Arabia showed an MRSA prevalence of 11% among CF patients, which was acquired at a mean age of 10.4 ± 7.2 years. That study also noted an increasing trend in MRSA infection with 79% of positive cultures occurring between 2010–2016 compared to 26% between 2002–2009.[22]

Several risk factors for early *P. aeruginosa* acquisition have been reported in the literature. A study in the USA by Maselli et al,[11] showed an association between early *P. aeruginosa* acquisition and female sex, homozygous deltaF508 mutation, co-infection with MSSA, and length of hospital stay. In our study, male patients had early *P. aeruginosa* acquisition. There was no statistically significant difference in CFTR genotype between the early and late *P. aeruginosa* groups.

In a study examining the potential role of social interaction as a risk factor for early *P. aeruginosa* infection, the interaction between a younger patient and an older CF patient was identified a risk factor.[16] Other studies showed that CF siblings can have *P. aeruginosa* cross-infection.[23,24] In our study, the presence of a sibling with CF was not a statistically significant risk factor for early acquisition.

Few environmental factors have been studied previously to address the causes of *P. aeruginosa* infections. The Morbidity and Mortality Weekly Report of the Centers for Disease Control and Prevention surveillance for waterborne disease outbreaks in the US (1993–1994) revealed that water sources, such as hot tubs and swimming pools, are sources of *P. aeruginosa* infections.[25] Another study showed that jacuzzis and hot tubs had the highest sources of *P. aeruginosa* infections among the studied water sources.[26] These parameters could not be studied in our study, but there was no relationship between demographic region and early acquisition.

In an adult study, it was noted that in patients with chronic obstructive pulmonary disease, pathogenic bacteria were isolated from the nebulization sets, which includes *P. aeruginosa* along with other pathogens.[27] This is a possible risk factor in our population; however, due to the retrospective nature of our study, it was not possible to retrieve such data.

There are several limitations to our study including its retrospective design leading to the risk of missing data. Additionally, we did not control for variations in airway sampling methods. Some of the possible risk factors, such as healthcare facility visits before diagnosis or water contamination, could not be studied. We recommend future prospective studies in Oman addressing these 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 demonstrated an early acquisition of *P. aeruginosa* and its predominance across all age groups. Among the studied risk factors, only the male sex showed a significant association with early acquisition. Early lower airway sampling with bronchoalveolar lavage for early *P. aeruginosa* detection and eradication could be considered by CF healthcare providers. Further studies are needed to investigate the environmental risk factors for early *P. aeruginosa* acquisition in Oman.

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Disclosure

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