International Journal of Contemporary Pediatrics
Fayaz A et al. Int J Contemp Pediatr. 2023 May;10(5):716-720
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20231149

Original Research Article

Pulmonary hypertension and the common organisms present in the sputum culture in children with cystic fibrosis

Aakifa Fayaz[1], Elmira Haji Esmail Memar[2], Vaseefat Ul Zehra[1], Naseer Yousuf Mir[3]*

[1]Department of Paediatrics, Tehran University of Medical Sciences, Iran
[2]Department of Paediatrics, Tehran University of Medical Sciences, Iran
[3]Department of Paediatrics, Government Medical College Srinagar, Jammu and Kashmir, India

Received: 21 March 2023
Revised: 17 April 2023
Accepted: 18 April 2023

***Correspondence:**
Dr. Naseer Yousuf Mir,
E-mail: mirnasirgmc@gmail.com

ABSTRACT

Background: Cystic fibrosis is an autosomal recessive genetic defect that affects multiple organs in the body. These patients present with progressive obstructive lung disease, sinusitis, exocrine pancreatic insufficiency and male infertility. The respiratory tract of these patients is more vulnerable for bacterial colonization, most commonly *Pseudomonas aeruginosa*, *Hemophilus influenza* and *Staphylococcus aureus*. There is a possibility of pulmonary hypertension development in these patients due to alveolar hypoxia alongside chronic systemic inflammatory response causing endothelial dysfunction.
Methods: This was a descriptive cross-sectional study which studied 109 cystic fibrosis patients admitted to CMC, Tehran in 2 years.
Results: In this study 109 patients were studied. 35 patients (32.1%) were <1 year of age, 11 patients (10.1%) were 1-5 years of age, 26 patients (23.9%) were 5-10 years of age and 37 patients (33.9%) were >10 years of age. 61 patients (56%) were females and 48 patients (44%) were males. The most common organisms encountered in sputum culture were *Staphylococcus aureus* (23.9%), *Pseudomonas aeruginosa* (18.3%) and *Candida albicans* (11.9%). Pulmonary arterial hypertension was present in 24.7% of the target population, out of which 22.9% were having mildly elevated PAH and 1.8% had severely high PAH.
Conclusions: The most common organism seen is *S. aureus* followed by *P. aeruginosa*. A significant number of patients presented with mildly elevated PAH and some with severely high PAH.

Keywords: Cystic fibrosis, Micro-organisms, Pulmonary hypertension

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder that affects the exocrine gland function that is most commonly seen in Northern European descent. It is a chronic disease that presents with chronic sino-pulmonary infections as well as pancreatic insufficiency. The usual cause of death remains end-stage lung disease.[1,2] It results from a genetic mutation on chromosome 7 that involves the CFTR protein.[1] Decreased muco-ciliary clearance alongside an altered ion transport make the respiratory tract more vulnerable for bacterial colonization, most commonly *P. aeruginosa*, *Haemophilus influenzae*, and *S. aureus*.[3] Pulmonary hypertension has a complex pathophysiology, but alveolar hypoxia alongside chronic systemic inflammatory response that causes endothelial dysfunction have been implicated by far.[4] CFTR defect is considered to cause 2 significant events in the pulmonary vasculature, those being: increased vascular cell

proliferation and reduced PA relaxation.[5] CF patients with pulmonary hypertension (PH) are at increased risk of death associated with advanced lung disease.[4] Alongside the established organisms-*P. aeruginosa*, *Burkholderia cepacia* and *S. aureus*, other novel gram-negative non-fermenter bacteria and non-tuberculosis *Mycobacteria* are now considered to be highly significant. Air sampling and analysis of cough aerosols has provided evidence for potential for airborne spread.[6] Most commonly associated bacteria with infection in CF patients are *S. aureus*, *H. influenza*; there are other opportunistic pathogens as well, like *P. aeruginosa*, *Stenotrophomonas maltophila* and *Achromobacter xylosoxidans* (nosocomial), *Burkholderia cepacia* complex, *Burkholderia gladioli*, *Ralstonia species*, *Cupriavidus* species and *Pandoraea* species.[7,8] On comparing the culture results on first and the last visits, prevalence of *P. aeruginosa* had increased from 34% to 53% and a decrease in prevalence of *S. aureus* and *H. influenza*.[9,10]

The recognition of PH may provide prognostic value and an opportunity for treatment. The main aim of this study was to determine the frequency of PH and the common organisms present in the sputum culture taken from CF patients that referred to Children Medical Center from March 2020 to March 2022. The ethical approval was provided by the Ethics Committee of the hospital. The privacy of the patients was well protected.

METHODS

It was a descriptive, cross-sectional, retrospective study conducted over a period of two years. Children with CF admitted to Children Medical Center, Tehran, from March 2020 to March 2022 were selected for the study. From the medical records of CF patients who were admitted to CMC during this period, the sputum culture reports and pulmonary pressures were analyzed. A total of 109 children were chosen by non-probable or convenient sampling method.

Inclusion criteria

All the patients referring to the Children Medical Center with diagnosed CF and with documented culture results and PAP (PAP) were included.

Exclusion criteria

CF patients referring to CMC with incomplete data record were excluded.

Statistical analysis

The collected data of 109 samples, with the diagnosis of CF and documented culture results and PAP over a period of March 2020 to March 2022, was entered into SPSS statistical software. The frequency command was used to determine the frequency of data. To describe qualitative variables, the number and percentage and quantitative variables, mean and standard deviation were used, if the distribution of variables was normal. If the data was not normal, the median and inter-quarter range (IQR) was used.

To compare the means of quantitative variables in qualitative subgroups, independent t test and Chi square test were used and in non-parametric conditions, U-man Whitney was used. Also, ANOVA command was used to compare the means of quantitative variables in several independent groups.

RESULTS

The total number of subjects studied were 109, divided in 2 age groups, <3 years of age and those >3 years of age. 61 patients (56%) were females and 48 patients (48%) were males as shown in Table 1.

On evaluating the sputum culture of patients, 36 patients (33%) had a culture positive for normal flora and 73 patients (77%) had a positive result for organisms other than the normal flora. The most common organisms that were encountered were *S. aureus* in 31 patients (28.5%) >*P. aeruginosa* in 29 patients (26.6%) >*Candida* in 16 patients (14.6%) and several combinations of the above-mentioned organisms.

In patients of age <3 years, the common pathogens were: *S. aureus* in 7 patients (17.9%) >*Candida* in 6 patients (15.4%) >*P.aeruginosa* in 3 patients (7.7%). In > 3-year-olds, the common pathogens were: *S. aureus* in 19 patients (27.1%) >*P. aeruginosa* in 17 patients (24.3%) >*Candida* in 7 patients (10%) (Table 2).

When considering the cumulative prevalence of *S. aureus* and *P. aeruginosa* in the study population, in the age group of <3 year old, a total of 10 patients (25.6%) had *S. aureus* in their sputum cultures and 7 patients (18%) had *P. aeruginosa* in their culture. In >3 years of age, 22 patients (31.4%) had cultures positive for *P. aeruginosa* and 21 patients (30%) had positive culture for *S. aureus*. The mentioned percentages also incorporate the cultures that were positive for both *S. aureus* and *P. aeruginosa* (Table 3). On analyzing the obtained data using Chi square, the p value obtained was 0.011. This means that the variation of organisms with respect to age is significant, with *S. aureus* being the most common organism in <3-year-olds and *P. aeruginosa* as the commonest organism in >3-year-olds.

On considering the cumulative prevalence of *S. aureus* and *P. aeruginosa* in the study population, among females, *P. aeruginosa* was seen in 19 patients (31.1%) and *S. aureus* was seen in 16 patients (26.2%). While as in males, *S. aureus* was seen in 15 patients (31.3%) *P. aeruginosa* in 10 patients (20.6%). To test the variability of organisms on the basis of gender, a Chi square test was performed and the p value was found to be 0.584. Hence,

gender doesn't play a significant role in the variability of frequency of organisms in the cultures of CF patients.

In this study, 27 patients (24.7%) had an elevated PAP, out of which 25 patients (22.9%) had mildly elevated PAP and 2 patients (1.8%) had severely high PAP (Table 4). A variability with age in consideration was apparent from the data, with 25 out of the 27 subjects with elevated PAP lying in the >3-year age group, and this finding was found to be significant (with a p value of 0.008). On further evaluation, the prevalence of PH showed notable peaks in 1-5 years age group and in those with age >10 years.

On the basis of gender, females had higher frequency of elevated PAP, as 18 females (29.5%) had elevated PAP in contrast to only 9 males (18.8%). Out of a total of 61 females, 18 females (29.5%), had an elevated PAP. The female gender predisposition to acquire higher PAP was not found to be significant (p value=0.267).

Table 1: Number and percentage of children in different age groups.

Age groups		Frequency	Percent	Valid percent	Cumulative percent
Valid	1.00	39	35.8	35.8	35.8
	2.00	70	64.2	64.2	100.0
	Total	109	100.0	100.0	

1=group 1, <3 years; 2=group 2, >3 years.

Table 2: Frequency of organisms on the basis of age.

New age organism in sputum culture crosstabulation			Organism in sputum culture			
			Candida	*Pseudomonas aeruginosa*	*E. coli*	Normal flora
New age	1.00	Count	6	3	1	17
		% within new age	15.4	7.7	2.6	43.6
	2.00	Count	7	17	2	19
		% within new age	10.0	24.3	2.9	27.1
Total		Count	13	20	3	36
		% within new age	11.9	18.3	2.8	33.0
New age organism in sputum culture crosstabulation			Organism in sputum culture			
			S. aureus	*S.aureus* and *P.aeruginosa*	*C. albicans* and *P. aeruginosa*	*C. albicans* and *S. aureus*
New age	1.00	Count	7	2	0	0
		% within new age	17.9	5.1	0.0	0.0
	2.00	Count	19	1	2	1
		% within new age	27.1	1.4	2.9	1.4
Total		Count	26	3	2	1
		% within new age	23.9	2.8	1.8	0.9
New age organism in sputum culture crosstabulation			Organism in sputum culture			
			E. coli and *P. aeruginosa*	*P. aeruginosa* and *Stenotrophomonas maltophila*	*K. pneumoniae*	*K. pneumoniae* and *P. aeruginosa*
New age	1.00	Count	0	0	1	1
		% within new age	0.0	0.0	2.6	2.6
	2.00	Count	1	1	0	0
		% within new age	1.4	1.4	0.0	0.0
Total		Count	1	1	1	1
		% within new age	0.9	0.9	0.9	0.9
New age organism in sputum culture crosstabulation			Organism in sputum culture	Total		
			P. aeruginosa, E. coli, S. aureus			
New age	1.00	Count	1	39		
		% within new age	2.6	100.0		
	2.00	Count	0	70		
		% within new age	0.0	100.0		
Total		Count	1	109		
		% within new age	0.9	100.0		

Table 3: Cumulative prevalence of organisms on the basis of age.

Age group organism group cross tabulation			Organism group				Total
			Staph	*Pseudom*	Other	Both	
Age group	1.00	Count	7	4	25	3	39
		% within age group	17.9	10.3	64.1	7.7	100.0
	2.00	count	20	21	28	1	70
		% within age group	28.6	30.0	40.0	1.4	100.0
Total		count	27	25	53	4	109
		% within age group	24.8	22.9	48.6	3.7	100.0

Table 4: The variability of PAP in different age groups.

New age PAP crosstabulation			PAP			Total
			<25 mmHg, normal	> 25 mmHg, mildly high	Severely high	
New age	1.00	Count	36	3	0	39
		% within new age	92.3	7.7	0.0	100.0
	2.00	Count	46	22	2	70
		% within new age	65.7	31.4	2.9	100.0
Total		Count	82	25	2	109
		% within new age	75.2	22.9	1.8	100.0

DISCUSSION

In a study done in 2003 by Santana et al in Bahia, Brazil, data from 69 patients was collected from medical records. The results were 36.2% *P. aeruginosa*, 28.9% *S. aureus*, 4.3% *K. pneumoniae*, 1.5% *H. influenzae*, 1.5% *E. coli*, 1.5% *S. maltophila* and in 27.5% the flora was normal. The prevalence of *P. aeruginosa* was 83% in less than 2-year-old patients which demonstrated early colonization.[11]

The study performed by Guliyeva et al in Turkey, that was published in Klin Padiatr in September 2021, involved 30 mild CF pediatric patients and 30 healthy children. These children were selected with similar demographics. The echocardiography parameters showed notably elevated PAP in CF patients in comparison with the control group.[12] Among the sample population, the most common CXR finding was bronchiectasis, as seen in 33 patients (30.3%). 40 out of 109 (36.7%) needed NIV during their hospitalization and only 8 patients (7.3%) needed intubation. 21 patients (19.3%) required to be admitted into the ICU. 6 out of the 109 patients (5.5%) had a positive blood culture while the other 103 patients (94.5%) had a negative blood culture. The organisms in the positive cultures were *P. aeruginosa* in 5 cultures and 1 culture was positive for *C. albicans*. 106 patients (96.4%) had insufficient quantity of fecal elastase and 3 patients (2.7%) had sufficient quantity of elastase.

Limitations

Limited time duration for the conduction of study was the limitation.

CONCLUSION

CF is an incurable disease that has seen significant improvement in recent times in terms of outcome. Pulmonary artery hypertension is one of the several complications that these patients suffer from. On a similar note, as these patients are more vulnerable to the colonization of micro-organisms in their respiratory tracts, they suffer from recurrent infections and hospital admissions. This study parallelized the already established dominance of *S. aureus* and gram-negative bacteria like *P. aeruginosa* in CF patients, and also the emergence of *Pseudomonas* (increasing prevalence from 18% to 31.4%) as a cause of severe morbidity with increasing age. The variability of organisms on the basis of age was found to be significant in this study. Parallel to the obtained organisms in sputum cultures, cloxacillin (69.3%) and vancomycin (56.4%) were the most frequently used antibiotics in <3-year-olds, for the sake of coverage against the most common organism, *S. aureus*. And in >3-year-olds, the adequate coverage was obtained by ceftazidime (92.9%) and amikacin (94.3%), alongside cloxacillin and vancomycin, to cover *P. aeruginosa* alongside *S. aureus*.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Fayaz A, Memar EHE, Zehra VU, Mir NY. Pulmonary hypertension and the common organisms present in the sputum culture in children with cystic fibrosis. Int J Contemp Pediatr 2023;10:716-20.