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The Most Common Causes of Bacterial Infections in Children with Cystic Fibrosis

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SUMMARY: Background: Cystic fibrosis is hereditary, autosomal recessive, multi-systemic disease. Defect of Cystic Fibrosis Transmembrane Regulator on 7th chromosome, leads to secretion of sticky viscous and thick mucus, which obstructs secretory ducts (respiratory and digestive tracts the most), and thus creates favorable conditions for growth of pathogenic bacteria which cause infections. The aim of this work is to investigate the most common pathogenic bacteria which cause bacterial infections in children affected by cystic fibrosis and which therapeutic protocols were used.

Materials and Methods: A retrospective study included 21 pediatric patients hospitalized in the department of pediatric pulmonology, Clinical Center University of Sarajevo. The study involved nasopharyngeal swab, deep sputum and blood for blood culture, sampled from hospitalized patients. The bacteria were isolated using standard procedures.

RESULTS: Most commonly isolated pathogens from respiratory tract were*Pseudomonas aeruginosa*(57,1%),somewhat less*Hemophilus influenzae* (42,9%) and*Staphylococcus aureus* (42,9%).The least isolated was*Streptococcus pneumoniae* (28,6%). In the largest number of patients (33.3%), two types of bacteria were isolated. In the same percentage (26.7%) we had patients with one type of bacteria isolated, as well as patients with 3 types of bacteria. In the smallest number of patients (13.3%), as many as 4 types of bacteria were isolated.

CONCLUSION: The most commonly isolated bacteria was*Pseudomonas aeruginosa*.

KEY WORDS: Bacterial infection, cystic fibrosis, pediatric population, antibiotics

I. INTRODUCTION

Cystic fibrosis (CF) is an inherited disorder that causes severe damage to the glands with external secretion in digestive and respiratory systems and other organs.This disease that shortens life affects more than 70,000 individuals worldwide [1]. Certain records of the "children of the salty kiss" were recorded more than five centuries ago. The disease was first described by Dr. Andersen (1938 years). Her research included a group of children with chronic diarrhea and frequent pneumonia, and for the first time linked the symptoms of digestive and lung disease into a completely new pathological concept – CF [2]. It is an autosomal recessive disease caused by mutation in the gene called the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), and the product of this mutation is CFTR protein dysfunction. CFTR- protein is a glycoprotein that transmits anions (negative ions) by binding energy and hydrolysis of the molecule. So far, over 2000 mutations in the CFTR-gene have been detected, of which about 200 cause CF [3]. CFTR dysfunction causes chronic mucus obstruction, neutrophilic inflammation and bacterial infection in airways [4].The defect causes an increase in the resorption of sodium and water from the lumen into the cells. A disorder of salt metabolism in cells occurs. The ionic composition of glandular mucus changes, which becomes sticky and tough, thus obstructing the excretory ducts, and in the respiratory system causes the accumulation of mucus that remains inside the respiratory tract and thus allows the creation of a suitable environment for bacteria to multiply and consequently cause infection, due to weakening of the immune system[5,6,**7**].Deficits in the immune response due to CFTR dysfunction result in a predisposition to acute and chronic lung infections with opportunistic pathogens. CF lung disease begins during infancy. Bacterial infection induces an intense neutrophilic response that contributes to airway injury [8,9]. CF airway infections are frequently polymicrobial. Pathogens that are most commonly detected include *P. aeruginosa*, *S. aureus*and *Aspergillus* spp.[10,11]. The disease is incurable and unfortunately, shows a very poor prognosis leading to the inevitable worsening from severe general weakness, eventually to death due to a combination of complications of respiratory failure and heart failure. Due to such a course of the disease,

patients died in early childhood for a long time. Antibiotic therapy is applied in the treatment of these infections, but there is a major problem of bacterial resistance to many antibiotic groups of drugs [12].The life expectancy of a child born with CF has improved steadily, largely because of advances in disease surveillance and more aggressive treatment strategies. Nevertheless, patients with CF die too young, with much of the early morbidity and mortality from CF resulting from progressive airway involvement[12].

II. MATERIAL AND METHODS

The study is retrospective and was conducted at Clinical center University of Sarajevo over a period of for years from 2014 to 2018. The study included 21 pediatric patients, from 3 months to 18 years old, who were hospitalized in the pulmonology department of the pediatric clinic.Patients were diagnosed with basic CF disease but also with other accompanying respiratory diseases such as *bronchopneumonia*, *bronchitis obs*., *respiratory insufficiency*, *bronchiolitis*, *bronchiectasis*, *ileus meconialis*, *cirrhosis hepatis*, *malnutrition*, *vomitus*, *pulmonary infiltration*, *hemoptysis* and *anemia*. The study involved nasopharyngeal swab and sputumwhich were collected from patients.After collection of samples from patients, were transported to the microbiological analysis. Bacteriological analysis of swab and sputum samples included microscopic identification, cultivation, standard biochemical testing and antimicrobial susceptibility testing. The data used were taken from the medical records (hospital protocols) of the patients included in the study. Access to medical documentation has been approved by the Organizational Unit of the Service for Science and Scientific Research of the Clinical Center of the University of Sarajevo. We used the results of biochemical and microbiological laboratory.

The sociodemographic and clinical data of the study participants were summarized using descriptive statistics. The results of the analysis are presented tabularly and/or graphically by number of cases, percentage, arithmetic mean with standard deviation and value range. Difference testing was performed using one-way analysis of variance (ANOVA) and a chi-square test with Yate's correction for small samples. Test results were considered significant at the 95% confidence level or with $p < 0.05$. The analysis was performed using the statistical package for biomedical research MedCalc v12.3 (Antwerp, Belgium) and Microsoft Excel 2016 (Richmond, USA).

III. RESULTS

Of a total of 21 patients included in the study, 15 (71,4%) were male and 6 (28,6%) females. The age of the participants ranged from 3 months to 18 years (mean and standard deviation: 10.3 ± 5.5). Additionally, more than half of them were above ten years of age (52.4%). The first or second hospitalization was noted in most patients, 17 (76.4%), after hospitalization most, 16 (76.2%), were recovered (Table 1).

Table 1. Demographic characteristics of the study participants (n = 21).

Characteristics Frequency	**Percentage(%)**	
Gender		
Male	15	71,4
Female	6	28,6
Age groups		
≤10 years	11	52,4
11–18 years	10	47,6
Number of hospitalizations		
≤2	17	76.4
3-12	4	23.6
Treatment outcome		
Recovered	16	76.2
Without improvement	2	9.5
Transferred to another department	2	9.5
Mortality	1	4.8

Out of a total of 21 patients, in 6 (28,6%) of them did not isolate any bacteria. Pathogenic bacteria were isolated insamples from 15 patients (71,4%). The following pathogens were identified: *Pseudomonas aeruginosa*, with a dominance of 57,1%, followed by 42,9% of *Hemophilus influenza*, 42,9% of *Staphylococcus aureus* and 28,6% of *Streptococcus pneumonia*. (Table 2, Figure 1).

Table 2. Number of patients with negative and positive samples

		N	%
without bacterial isolates	Patients	6	28,6
with bacterial isolates	Patients	15	71,4%
total		21	100

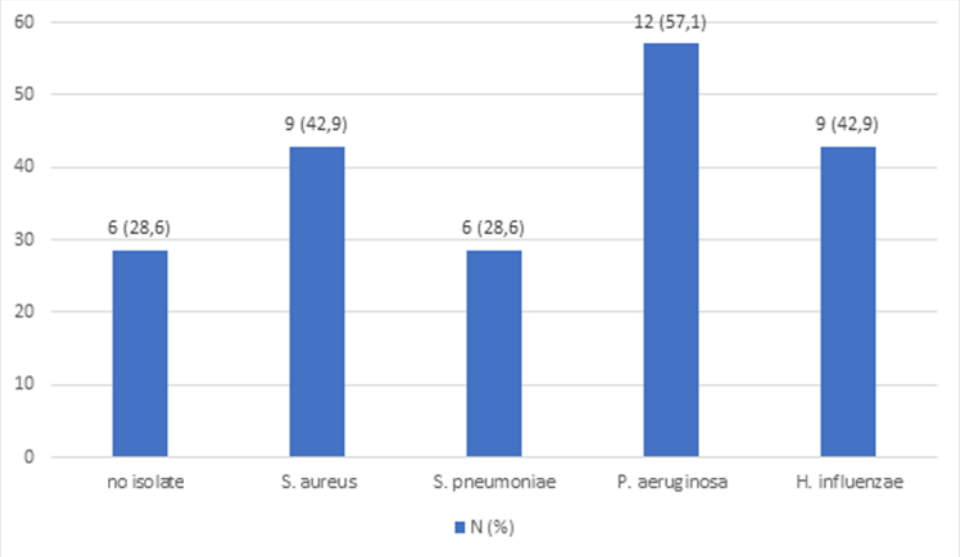

Figure 1.Rate of isolated bacteria

Infections with two or more bacteria have been reported in some patients. In the five patients (33.3%), two types of bacteria were isolated. In the same percentage (26.7%) we had 4 patients with one type of bacteria isolated, as well as patients with 3 types of bacteria. In the smallest number of patients 2 (13.3%), as many as 4 types of bacteria were isolated. (Figure 2).

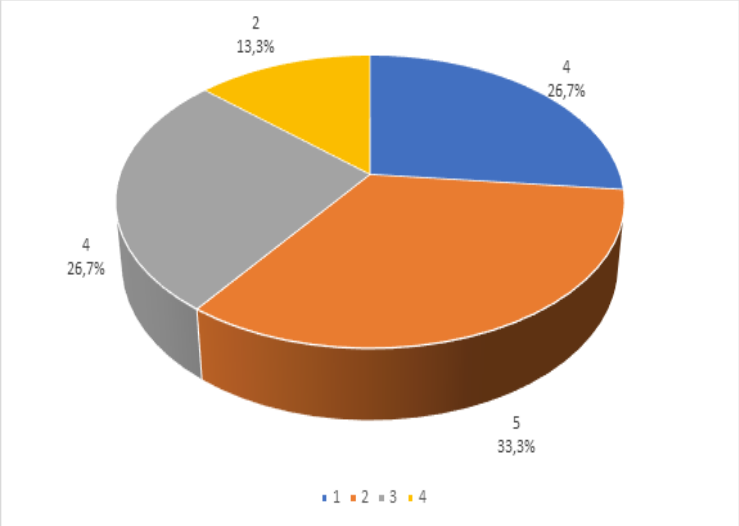

Figure 2. Various combinations of pathogens

Figure 2 shows the number of different combinations of pathogenic bacteria isolated in patients. *P. aeruginosa* was isolated as a single pathogen in 3 patients, in combination with *H. influenzae* in 2 (9.5%), or *S. pneumoniae* in 1 (4.8%) or *S. aureus* in 2 (9.5%). It has also been isolated in combination with 2 or 3 different pathogens. Other microorganisms were also isolated, but in a smaller percentage.

From Table 3 it is clear that the oldest were patients with isolates of *H. influenzae* with an average age of 11.3 ± 5.2 years (range 3-18 years), and the youngest patients without isolates with an average age of 9, 3 ± 5.7 years (range 3-18 years). Statistical analysis by one-way analysis of variance (ANOVA) shows that there is no significant difference in age compared to isolates (p> 0.05).

Table 3. Average age of subjects according to isolates

		No isolates	*S. aureus*	*S. pneumoniae*	*P. aeruginosa*	*H. influenzae*	Total
Year	$\bar{X}$	9,33	10,33	10,33	10,42	11,33	10,19
	Standard deviation	5,72	4,50	5,85	5,28	5,20	5,35
	Minimum	3,00	3,00	3,00	1,00	3,00	1,00
	Maximum	18,00	15,00	18,00	18,00	18,00	18,00

Table 4 shows that the lowest number of hospitalizations was in patients without isolates, and patients with*S. pneumoniae* had the highest number of hospitalizations. According to statistical analysis, no significant difference in the number of hospitalizations compared to isolated species of bacteria (p> 0.05).

Table 4. Number of hospitalizations according isolates

		No isolates	*S. aureus*	*S. pneumoniae*	*P. aeruginosa*	*H. influenzae*	Total
Number of hospitalization	$\bar{X}$	1,33	2,56	5,33	3,25	3,11	2,43
	Standard deviation	,82	3,57	4,37	3,67	3,86	2,93
	Minimum	1,00	1,00	1,00	1,00	1,00	1,00
	Maximum	3,00	12,00	12,00	12,00	12,00	12,00

Table 5 shows that the duration of hospitalization differs statistically significantly in relation to the types of isolated bacteria. Patients with*S. pneumoniae* had the longest hospitalization - 69.7 ± 4.3 days, and the patients without isolates shortest 21.2 ± 5.3 days.

Table 5. The duration of hospitalization compared to isolates

		No isolates	*S. aureus*	*S. pneumoniae*	*P. aeruginosa*	*H. influenzae*	Total
During hospitalization	$\bar{X}$	21,17	22,67	69,67	41,67	38,78	31,19
	Standard deviation	5,26	7,44	4,25	5,40	5,36	4,67
	Minimum	8,00	4,00	7,00	4,00	7,00	4,00
	Maximum	42,00	122,00	139,00	139,00	139,00	139,00

Table 6. Antibioticsadministered to patients according to isolated microorganisms

		No isolates	*S. aureus*	*S. pneumoniae*	*P.aeruginosa*	*H. influenzae*	Total
Cephalosporins χ2=1,130; p=0,8894	N	4	4	3	7	4	13
	%	19,0	19,0	14,3	33,3	19,0	61,9
Penicillin'sχ2=1, 287; p=0,963	N	2	1	1	2	2	5
	%	9,5	4,8	4,8	9,5	9,5	23,8
Macrolidesχ2=2,9 81; p=0,5610	N	0	1	2	2	1	2
	%	0,0	4,8	9,5	9,5	4,8	9,5
Aminoglycosides χ2=1,968; p=0,7416	N	3	6	5	8	7	13
	%	14,3	28,6	23,8	38,1	33,3	61,9
Carbapenemsχ2= 5,014; p=0,2856	N	0	3	3	6	4	7
	%	0,0	14,3	14,3	28,6	23,8	33,3
Fluoroquinolones χ2=6,800; p=0,1468	N	0	0	2	4	1	4
	%	0,0	0,0	9,5	19,0	4,8	19,0

Table 6 shows that the statistical analysis does not show a significant difference between drugs from a certain group of antibiotics compared to isolated bacteria.

IV. DISCUSSION :

Cystic fibrosis (CF) remains the most common fatal inherited lung disease (4). In patients with cystic fibrosis, persistent bronchopulmonary infections of *S. aureus*, *P. aeruginosa* and several other pathogens occur, leading to chronic airway and systemic inflammation, tissue destruction, and respiratory failure [9].In our study we enrolled 21 pediatric patients (15 male and 6 females, 0-18 years old).Ramzey at al. in their extensive research had slightly more boys similar to our study[14].In the samples of our patients were isolated the most common *P. aeruginosa* - in 12 (57.1%) patients, *H. influenzae* in 9 (42.9%), *S. aureus* also in 9 (42.9%) and *S. pneumoniae* in 6 (28.6%) patients. Also, in our study, we had patients in whom two or more bacteria were isolated. The mean age according to the isolates showed that the oldest were patients with *H. influenzae* isolates with an average of 11.3 ± 5.2 years (range 3-18 years), and the youngest patients without isolates with an average of 9.3 ± 5.7 years (range 3-18 years), but there is no significant difference compared to isolates ($p > 0.05$).Also, there was no significant difference in the number of hospitalizations compared to isolated bacteria, but still the largest number of hospitalizations in patients with *S. pneumoniae* isolate. When we talk about the length of hospitalization, most days in the hospital have been patients with *S. pneumoniae* isolate (had the longest hospital stay 69.7 ± 4.3 days).*Pseudomonas aeruginosa* is the prominent bacterial pathogen in the cystic fibrosis (CF) lung and contributes to significant morbidity and mortality. Though *P. aeruginosa* strains initially colonizing the CF lung have a nonmucoid colony morphology, they often mutate into mucoid variants that are associated with clinical deterioration. Both nonmucoid and mucoid *P. aeruginosa* variants are often co-isolated on microbiological cultures of sputum collected from CF patients[15].We found *Pseudomonas aeruginosa*is the predominantly isolated species. Similar results with *P. aeruginosa* as the most frequently isolated microorganisms have been reported by the others [14, 15, 16, 17].In our study second most common isolated strain was *Staphylococcus aureus* (42,9%). Rutter at al. in their study isolated also *P. aeruginosa* (41%) and slightly less *S. aureus* (40%) [14, 18]. Abram et al. in their study have the most *H. influenza* isolate is in the age

group from 3 to 18 years, but in younger patients is mostly represented by *S. aureus*[19]. The most commonly detected organisms in the lower airways of young infants are *S. aureus* and *P. aeruginosa*, followed by *Aspergillus* species, *H. influenzae* and *S. pneumoniae*. Infants with lower airway infection generally do not always have respiratory symptoms. During infancy, infection with *P. aeruginosa*, *H. influenzae*, *S. pneumoniae* and *S. aureus* is associated with higher levels of inflammation than with a range of otherorganisms. Furthermore, inflammation increaseswith organism density and the number of speciesisolated[20].In our study, the results of antibiotic therapy used in the eradication of bacterial pathogens in respiratory infections showed that cephalosporins (33.3%), fluoroquinolones (19%) and carbapenems (28.6%) were most commonly used in isolates of *P. aeruginosa*, and aminoglycosides, macrolides and penicillinto patients with a combination of isolates of *P. aeruginosa*, *H. influenzae* and *S. pneumoniae*.All patients were treated with one or a combination of cephalosporins. In 52.4% only cefazolin was used, and up to 95.2% had up to 4 drugs included in the therapy (cefazolin, cephalexin, ceftazidime, ceftriaxone). Penicillin was administered to 23.8% of patients, of which 85.7% were covered by ampicillin, amoxicillin, and clavulanic acid therapy. Macrolides were used in 9.5% of patients(in 2 cases), aminoglycosides in 13 patients (amikacin in 12 patients, 1 patient had a combination of 3 drugs amikacin, tobramycin and gentamicin). Carbapenems were received by 7 patients (both imipenem and meropenem, and one patient was on therapy with both drugs). Fluoroquinolones were received by 4 patients (3 of them ciprofloxacin, and 1 received ciprofloxacin and levofloxacin). According to theBrazilian guidelines for the diagnosis and treatment of cystic fibrosis for mild exacerbations recommended use oral antimicrobialagents (according to of the last respiratory secretion culture result). For *P. aeruginosa*, the combination of two or more antibiotics (usually a beta-lactam and an aminoglycoside) is recommended.Treatment time for an acute pulmonary exacerbation depends on clinical response, with the recommendation being 8 to 14 days [21].

V. CONCLUSION

Cystic fibrosis (CF) is characterized by recurrent airway infection, inflammation and progressive decline in lung function.The possibility of early recognition of patients with milder symptoms and form of the disease, timely therapeutic intervention, and better control of symptoms and prophylaxis of occurrence of severe complications is all together possible extension of the lifespan of patients up to 40 years of age, which is a great success.Thanks to today people with CF often have a better quality of life than they had people with CF in previous decades.

Conflict of interest : The authors have declared no conflict of interest.

REFERENCES

1. Strug LJ, Stephenson AN, Panjwani N and Ann Harris.Recent advances in developing therapeutics for cystic fibrosis.*Human Molecular Genetics* 2018; 13:173–186.
2. Andersen, D.H. Cystic fibrosis of the pancreas and its relation to celiac disease: A clinical and pathologic study. *Am. J. Dis. Child*. 1938; 56:344–399.
3. Ogden HL, Kim H, Wikenheiser-Brokamp KA, Naren AP and Mun KS.Cystic Fibrosis Human Organs-on-a-Chip.*Micromachines*2021;doi:org/10.3390/mi12070747.
4. Mall1 MA and Hartl D. CFTR: cystic fibrosis and beyond.*Eur Respir J* 2014; 44:1042–1054.
5. Pittman JE, Wylie KM, Akers K, Storch GA, Hatch J, Quante J.*et al*.Association of Antibiotics, Airway Microbiome, and Inflammation in Infants with Cystic Fibrosis.*AnnalsATS*2017; 14:1549-1555.
6. Conese M and Assael BM. Bacterial infections and inflammation in the lungs of cystic fibrosis patients.*Pediatr Infect Dis J* 2001;20:207–13.
7. Cabrini G, Rimessi A, Borgatti M, Lampronti I,Finotti A, Pinton P*at al*.Role of Cystic Fibrosis Bronchial Epithelium in Neutrophil Chemotaxis.*Frontiers in Immunology*2020; doi:org/10.3389/fimmu.2020.01438.
8. Malhotra S, Hayes D, Wozniakb DJ. Cystic Fibrosis and Pseudomonas aeruginosa: the Host-Microbe Interface.*Clinical Microbiology Review*s 2019; doi.org/10.1128/CMR.00138-18.
9. Cantin AM,Hartl D, Konstan MW, Chmiel JF.Inflammation in cystic fibrosis lung disease: Pathogenesis and therapy. *Journal of Cystic Fibrosis* 2015; 14:419–430.
10. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis.*Nat Rev Dis Primers*(available in PMC 2020 February 25), doi:10.1038/nrdp.2015.10.
11. Zemanick ET, Harris JK, Wagner BD, Robertson CE, Sagel SD, Stevens MJ e*t al*.Inflammation and Airway Microbiota during Cystic Fibrosis Pulmonary Exacerbations2013;PLOS ONE8(4):e62917.
12. Taccetti G, Francalanci M, Pizzamiglio G, Messore B, Carnovale V,Cimino G *et* al.Cystic Fibrosis: Recent Insights into Inhaled Antibiotic Treatment and Future Perspectives.*Antibiotics* 2021; doi.org/10.3390/antibiotics10030338.
13. Pittman JE and Ferkol TW.The Evolution of Cystic Fibrosis Care. CHEST 2015; 148:533-542.

14. RamseyKA, Hart E, Turkovic L, Padros-Goossens M, Stick SM, Ranganathan SC.Respiratory infection rates differ between geographically distant paediatric cystic fibrosis cohorts.*ERJ Open Res* 2016;doi: 10.1183/23120541.00014-2016.
15. Coburn B, Wang PW, Caballero JD, Clark ST, Brahma V,Donaldson S. Lung microbiota across age and disease stage in cystic fibrosis. SCIENTIFIC REPORTS 2015; doi: 10.1038/SREP10241.
16. Malhotra S, Hayes DJr, Wozniaka DJ.Mucoid Pseudomonas aeruginosa and regional inflammation in the cystic fibrosis lung.*J Cyst Fibros* 2019; 18:796–803.
17. Malhotra S, Hayes DJr, Wozniak DJ.Cystic Fibrosis and Pseudomonas aeruginosa: the Host-Microbe Interface.*Clinical Microbiology Reviews*2019; doi.org/10.1128/CMR.00138-18.
18. Rutter WC, Burgess DR, Burgess DS. Increasing Incidence of Multidrug Resistance Among Cystic Fibrosis Respiratory Bacterial Isolates.*Microbial drug resistance*2017; 23:51-55.
19. Abram M, Banac S, Rožmanić V. Microbiology of respiratory samples from children with cystic fibrosis. *Medicina* 2007;43:34-38.
20. Schultz A. and Stick S.Early pulmonary inflammation and lung damage in children with cystic fibrosis.*Respirology*2015; 20:569–578.
21. Athanazio RA, Filho LVRF, Vergara AA, Ribeiro AF, Riedi CA, Procianoy EFA *et al*. Brazilian guidelines for the diagnosis andtreatment of cystic fibrosis. *Bras Pneumol*. 2017;43(3):219-245.