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Changes in Antibiotic Resistance of Children with Cystic Fibrosis and Impact on Clinical Outcomes

Kistik Fibrozisli Çocuklarda Antibiyotik Direncindeki Değişimler ve Klinik Sonuçlar Üzerindeki Etkisi

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ABSTRACT

Aim: Antibiotics have an important role in the treatment of cystic fibrosis (CF) lung disease. Antibiotic resistance, especially multidrug resistance (MDR), increases in CF. This study aimed to determine whether there is a change in antibiotic resistance of pathogens isolated from the respiratory tract specimens of CF patients and to evaluate the relationship between the antibiotic resistance and patients' clinical status and pulmonary function.

Material and Methods: Thirty-nine CF patients with identified microorganisms in respiratory tract specimens from August 2010 through December 2016 were included in the study. 333 respiratory cultures taken from 39 CF patients were analyzed retrospectively.

Results: Methicillin-sensitive *S. aureus* (MSSA) was isolated from 122 (31.0%) cultures, *P. aeruginosa* from 97 (24.7%), and methicillin-resistant *S. aureus* (MRSA) from 22 (5.6%). The prevalence of MSSA (p=0.020) and MRSA (p=0.010) increased from 2010 to 2016, while the prevalence of *P. aeruginosa* and other microorganisms did not increase. MDR-*S. aureus* and MDR-*P. aeruginosa* prevalence did not change, but MRSA prevalence increased over the years (p=0.001). There was a significant relation between the antibiotic resistance and acute pulmonary exacerbations, pulmonary examination findings, loss in weight and height percentile. As the antibiotic resistance increased, FEV_1, FVC, FEV_1/FVC, PEF, and FEF_{25-75} were significantly decreased. The use of long-term azithromycin or inhaled antibiotics was not associated with antibiotic resistance.

Conclusion: In CF patients, resistance to antibiotics increased over the years. It is important to obtain respiratory tract cultures regularly and initiate rational antibiotic treatment based on culture results.

Keywords: Cystic fibrosis; multidrug resistance; respiratory cultures; antibiotic resistance.

ÖZ

Amaç: Antibiyotikler, kistik fibrozis (KF) akciğer hastalığının tedavisinde önemli bir role sahiptir. KF'de antibiyotik direnci, özellikle çoklu ilaç direnci (ÇİD) artmaktadır. Bu çalışmanın amacı, KF hastalarının solunum yolu örneklerinden izole edilen mikroorganizmaların antibiyotik direncinde bir değişiklik olup olmadığını belirlemek ve antibiyotik direnci ile hastaların klinik durumu ve akciğer fonksiyonları arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Ağustos 2010 ile Aralık 2016 tarihleri arasında solunum yolu örneklerinde mikroorganizma tespit edilen 39 KF hastası çalışmaya dahil edildi. 39 KF hastasından alınan 333 solunum kültürü geriye dönük olarak analiz edildi.

Bulgular: Metisiline duyarlı *S. aureus* (MSSA) 122 (%31,0), *P. aeruginosa* 97 (%24,7) ve metisiline dirençli *S. aureus* (MRSA) 22 (%5,6) kültürden izole edildi. MSSA (p=0,020) ve MRSA (p=0,010) prevalansı 2010'dan 2016'ya artarken, *P. aeruginosa* ve diğer mikroorganizmaların prevalansı artmamıştı. ÇİD-*S. aureus* ve ÇİD-*P. aeruginosa* prevalansı değişmemiş, ancak MRSA prevalansı yıllar içinde artmıştı (p=0,001). Antibiyotik direnci ile akut pulmoner alevlenme, akciğerde dinleme bulgularının varlığı, kilo ve boy persentil kaybı arasında anlamlı ilişki saptandı. Antibiyotik direnci arttıkça FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75} anlamlı olarak azalmıştı. Uzun süreli azitromisin veya inhale antibiyotik kullanımı ile antibiyotik direnci arasında ilişkili bulunmadı.

Sonuç: KF hastalarında antibiyotiklere karşı direnç yıllar içinde artmıştır. Düzenli olarak solunum yolu kültürlerinin alınması ve kültür sonuçlarına göre akılcı antibiyotik tedavisinin planlanması önemlidir.

Anahtar kelimeler: Kistik fibrosis; çoklu ilaç direnci; solunum kültürleri; antibiyotik direnci.

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INTRODUCTION

Cystic fibrosis (CF) is a hereditary, multisystem disease that affects the lungs, sweat glands, digestive system, and genitourinary system. Although it is a systemic disease, lung disease is the major cause of mortality and morbidity in CF (1). In addition to factors such as dietary regulation, changes in general care rules, increased use of highly effective modulator therapy, increased infection prevention and control strategies, and more effective use of antibiotics have important roles in the prolonged survival of patients with CF. Oral, parenteral, or inhaled antibiotics are administered based on individual patient assessments. The therapeutic objective is to minimize lower airway infection burden and ameliorate clinical manifestations alongside improving pulmonary function test (PFT) outcomes (2).

It is known that the most common microorganisms in childhood are *S. aureus* and *H. influenzae* within the initial 10 years of life, and transitioning to *S. aureus* and *P. aeruginosa* thereafter (3). In the recent data about CF patients, the most common microorganisms of all ages were methicillin-sensitive *S. aureus* (MSSA) with 50.2%, *P. aeruginosa* with 26%, *Nontuberculous Mycobacteria* with 10.3%, *Stenotrophomonas maltophilia* with 5%, *Achromobacter (Alcaligenes) xylosoxidans* with 2.4%, and *Burkholderia cepacia complex* with 1.3% (4).

Antibiotic resistance, especially multidrug resistance (MDR), is a major problem in CF. In patients with CF, MDR bacteria can predispose to pulmonary exacerbations, limit the efficacy of antibiotic therapies, and cause progression of lung disease (5). Meta-analyses have demonstrated that antibiotic resistance poses a significant challenge in the long-term management of CF patients, particularly concerning *P. aeruginosa* and *S. aureus*. Moreover, there is a concerning trend indicating a gradual decline in antibiotic susceptibility (6,7). MDR-*P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA) pose a distinct threat to patients with CF, as they are characterized by more severe lung disease, increased hospitalization rates, and higher mortality. Moreover, even after intravenous antibiotic administration for respiratory exacerbations caused by these pathogens, the lungs fail to return to pre-infection function (8). This study aimed to determine whether there is a change in antibiotic resistance of pathogens isolated from the respiratory tract specimens of CF patients over the years and to evaluate the relationship between the antibiotic resistance and patients' clinical status and pulmonary function.

MATERIAL AND METHODS

The records of the patients who were followed at the Division of Pediatric Pulmonology with the diagnosis of CF and their culture results were analyzed retrospectively. From the patients who were diagnosed with CF with at least two positive sweat test results, those who had regular follow-up and gave a respiratory tract sample for culture from which significant microorganisms were isolated between August 2010 and December 2016 were included. The protocol was approved by the Kocaeli University Ethics Committee (date: 06.02.2017, number: 2017/21).

Acute Pulmonary Exacerbation and Chronic Colonization

Acute pulmonary exacerbation is defined as a respiratory event requiring antibiotic treatment with at least 4 of 12 specific sign and symptom criteria which are increased cough, change in sputum production, hemoptysis (new or increasing), increased dyspnea, malaise, fatigue or lethargy, fever greater than 38 °C, anorexia or weight loss, sinus pain or tender-ness, change in sinus drainage, change in respiratory system examination, 10% or more decrease in PFT, radiographic changes suggestive of lung infection (9,10). Chronic colonization is considered to be established when more than 50% of respiratory tract cultures (at least 4 cultures per year) are positive for *P. aeruginosa* or MRSA taken in the last 1 year (11,12).

Respiratory Tract Specimens

Sputum samples were obtained from patients who could expectorate sputum. Nasopharyngeal aspirate (NPA) samples were taken from patients who could not expectorate sputum (13).

Evaluation of Samples in Microbiology Laboratory

In the microbiology laboratory, sputum specimens and NPA specimens are plated on eosin methylene blue agar, 5% sheep blood agar, and chocolate agar. Plates are incubated for 24-48 hours at 35±2 °C in a 5-10% CO_2 environment. The waiting time is 48 hours to say the culture is negative. For bacterial identification, matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is used, and VITEK® 2 is used for the antibiogram.

Classification of Antibiotic Resistance

According to the results of the antibiotic susceptibility test, samples were divided into 4 groups: non-resistant, single-drug resistant, two-drug resistant, and MDR. If the bacteria are susceptible to all classes of antibiotics studied by the microbiology laboratory, they are called non-resistant; if they are resistant to single antimicrobial categories, they are defined as single-drug resistant; if they are resistant to two antimicrobial categories, they are defined as two-drug resistant. MDR was defined as not being susceptible to one or more antimicrobial agents in three or more antimicrobial categories for all microorganisms. For the definition of MDR in *S. aureus*, all MRSA isolates are considered MDR due to resistance to a key antimicrobial agent (14).

Pulmonary Function Test

The PFT was performed in CF patients aged 6 years and older who can perform spirometry (Flowhandy ZAN 100, Germany). The PFT was performed during periods of clinical exacerbation. The procedure was performed according to the criteria of the standardization of spirometry 2019 update (15).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 20.0. Normality of distribution was assessed using the Kolmogorov-Smirnov test. Numerical variables were presented as mean±standard deviation, median (25^{th}-75^{th} percentiles), and categorical variables as frequency (percentages). Differences between groups for numerical variables with normal distribution were analyzed using one-way analysis of variance (ANOVA) and Tukey's post hoc test. For numerical variables not normally distributed, the Kruskal-Wallis and Dunn's multiple comparison tests were applied. Categorical variables were evaluated using the Monte Carlo chi-square analysis. The relationship between numeric variables was assessed using Spearman correlation analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among 52 patients followed with the diagnosis of CF, 4 patients did not have any significant microorganisms in respiratory cultures, and 9 patients did not come for regular follow-up visits. Therefore, the study was completed with 39 patients, of whom 17 (43.6%) were female. 333 respiratory tract samples with identified microorganisms in cultures were evaluated. There were 60 (18%) samples with multiple microorganisms. Therefore, there were 393 microorganisms identified in the respiratory tract samples. 100 (30%) samples were sputum, and 233 (70%) were NPA culture. The mean age of the patients was 95.5±54.1 months, and the mean age of the patients at the time of the diagnosis of CF was 16.5±4.0 months. It was observed that as the age at diagnosis decreased, the development of drug resistance increased (p=0.002, r=-0.155). Furthermore, the development of drug resistance was higher in males compared to females (p<0.001). In the follow-up of the 39 patients, MSSA was detected in 28 (71.8%), MRSA in 10 (25.6%), *P. aeruginosa* in 22 (56.4%), *H. influenzae* in 17 (43.6%), and *S. maltophilia* in 4 (10.3%) patients (Table 1). Additionally, in 8 (20.5%) patients, *P. aeruginosa* and MRSA were detected at different times.

Among the 393 microorganisms identified in 333 respiratory tract samples, the distribution of the microorganisms in order of frequency was MSSA in 122 (31.0%) samples, *P. aeruginosa* in 97 (24.7%) samples, *M. catarhalis* in 36 (9.2%) samples, and MRSA in 22 (5.6%) samples. The prevalence of MSSA increased from 28.9% (n=11) in 2010 to 32.0% (n=41) in 2016 (p=0.020, r=0.83). The prevalence of MRSA increased from zero in 2010 to 8.6% (n=11) in 2016 (p=0.010, r=0.87). *P. aeruginosa* was present at a rate of 26.3% (n=10) in 2010 and 27.3% (n=35) in 2016 (p=0.057, r=0.74). Although the prevalence of MSSA and MRSA increased from 2010 to 2016, there was no statistically significant difference in the prevalence of *P. aeruginosa* over the years. There was no significant increase in the prevalence of MDR-*S. aureus* (p=0.570) and MDR-*P. aeruginosa* (p=0.180) over the years, while the frequency of MRSA (p=0.001) increased. The number of cultures and percentages of MDR microorganisms over the years were presented in Table 2.

When the antibiotic susceptibility was evaluated, all MRSA strains were resistant to benzylpenicillin, ampicillin, aztreonam, cefepime, amikacin, and netilmicin. However, they were susceptible to ceftazidime, tobramycin, ciprofloxacin, levofloxacin, meropenem, colistin, linezolid, tigecycline, and vancomycin. In terms of *P. aeruginosa*, while 95.2% of the strains were susceptible to colistin, 81.2% to meropenem, 83.7% to ciprofloxacin, 88.6% to tobramycin, 70.8% to amikacin, 91.8% to ceftazidime, and 70% to piperacillin. All MSSA strains were resistant to

Table 1. The prevalence of each microorganism (n=39)

Microorganism	n (%)
MSSA	28 (71.8)
P. aeruginosa	22 (56.4)
M. catarhalis	19 (48.7)
H. influenzae	17 (43.6)
S. pneumoniae	13 (33.3)
MRSA	10 (25.6)
K. pneumoniae	8 (20.5)
E. cloacea	7 (17.9)
E. coli	5 (12.8)
A. baumannii	5 (12.8)
S. marcescens	4 (10.3)
Moraxella group	4 (10.3)
S. maltophiliae	4 (10.3)
P. fluorescens	2 (5.1)
E. faecium	2 (5.1)
B. cepacia	1 (2.6)

MSSA: methicillin-sensitive *S. aureus*, MRSA: methicillin-resistant *S. aureus*

Table 2. The number of cultures and percentages of MDR microorganisms by years, n (%)

Microorganism	2010	2011	2012	2013	2014	2015	2016	p	Total
MSSA	11 (28.9)	9 (20.0)	9 (27.3)	11 (36.7)	16 (33.3)	25 (35.2)	41 (32.0)	**0.020**	122 (31.0)
P. aeruginosa	10 (26.3)	7 (15.6)	7 (21.2)	7 (23.3)	12 (25.0)	19 (26.8)	35 (27.3)	0.057	97 (24.7)
M. catarhalis	3 (7.9)	5 (11.1)	4 (12.1)	2 (6.7)	7 (14.6)	6 (8.5)	9 (7.0)	0.500	36 (9.2)
S. pneumoniae	5 (13.2)	8 (17.8)	4 (12.1)	4 (13.3)	6 (12.5)	1 (1.4)	5 (3.9)	0.500	33 (8.4)
H. influenzae	4 (10.5)	4 (8.9)	1 (3.0)	4 (13.3)	2 (4.2)	4 (5.6)	10 (7.8)	0.460	29 (7.4)
MRSA	0 (0.0)	0 (0.0)	2 (6.1)	1 (3.3)	1 (2.1)	7 (9.9)	11 (8.6)	**0.010**	22 (5.6)
K. pneumoniae	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (1.4)	9 (7.0)	0.170	12 (3.1)
S. marcescens	1 (2.6)	6 (13.3)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.8)	0.480	10 (2.5)
E. cloacea	1 (2.6)	2 (4.4)	0 (0.0)	0 (0.0)	1 (2.1)	2 (2.8)	1 (0.8)	0.840	7 (1.8)
S. maltophilia	0 (0.0)	1 (2.2)	1 (3.0)	1 (3.3)	1 (2.1)	1 (1.4)	1 (0.8)	0.510	6 (1.5)
A. baumannii	1 (2.6)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	2 (2.8)	2 (1.6)	0.280	6 (1.5)
Moraxella group	0 (0.0)	0 (0.0)	2 (6.1)	0 (0.0)	1 (2.1)	0 (0.0)	1 (0.8)	0.510	4 (1.0)
E. coli	1 (2.6)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	0 (0.0)	0.600	4 (1.0)
P. fluorescens	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	0.140	2 (0.5)
E. faecium	0 (0.0)	1 (2.2)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.280	2 (0.5)
B. cepacia	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.360	1 (0.3)
Total	**38**	**45**	**33**	**30**	**48**	**71**	**128**		**393**

MDR: multidrug resistant, MSSA: methicillin-sensitive *S. aureus*, MRSA: methicillin-resistant *S. aureus*

ampicillin and ampicillin-sulbactam, but susceptible to amoxicillin-clavulanate, cefepime, cefazolin, ceftazidime, ceftriaxone, ceftazidime-sulbactam, amikacin, meropenem, and colistin. 209 microorganisms were identified in cultures obtained from patients colonized with MRSA and *P. aeruginosa*. There was no correlation between colonization and antibiotic resistance (p=0.080).

Thirty-five (89.7%) patients had genetic analysis, and the most common mutation was ΔF508 (42%). There was no difference between the ΔF508 mutation and antibiotic resistance (p=0.100). Patients' weight and height percentiles at the time of culture collection were noted. When the relationship between antibiotic resistance (one drug resistant, two drug resistant, MDR) development and percentile changes was evaluated, there was a statistically significant decrease in weight and height percentiles as antibiotic resistance increased (p=0.002, and p<0.001, respectively). There was a significant difference between antibiotic resistance and the presence of acute pulmonary exacerbation at the time of taking respiratory specimens (p=0.007). There was no significant relationship between having hypoxemia at the time of taking respiratory specimens and antibiotic resistance (p=0.080). It was observed that there was a significant difference between antibiotic resistance and the presence of wheezing, rales, or rhonchi on auscultation when the culture was taken (p=0.001).

Six (15.4%) patients had been diagnosed with the neonatal CF screening program. Antibiotic resistance was found to be higher in these patients who were diagnosed with newborn screening (p=0.004).

Sixty-nine microorganisms were obtained from the cultures of patients using long-term azithromycin treatment. There was no statistically significant relation between the long-term use of azithromycin in the past 6 months prior to culture collection (p=0.340), within the last year (p=0.450), and at any time in life (p=0.240) and the development of antibiotic resistance. Additionally, no significant relationship was found between azithromycin use and MRSA growth (p=0.080). However, a higher prevalence of MSSA colonization was observed in azithromycin users compared to non-users (p<0.001).

One hundred sixty-two microorganisms were obtained from the cultures of patients who used inhaled antibiotics. No significant relation was found between the use of inhaled antibiotics within the last 6 months prior to culture collection (p=0.320), within the last year (p=0.810), and at any time in life (p=0.330) and the development of antibiotic resistance.

The results of 47 PFTs performed simultaneously with the collection of respiratory tract cultures were evaluated. When PFT results were compared, a statistically significant decrease was observed in FEV_1 (p<0.001), FVC (p=0.003), FEV_1/FVC (p<0.001), PEF (p=0.002), and FEF_{25-75} (p=0.001) parameters as antibiotic resistance increased (Table 3).

DISCUSSION

Antibiotics have an important role in the treatment of CF lung disease. However, antibiotic resistance, especially MDR, is a significant problem. 333 respiratory cultures taken from 39 CF patients were analyzed retrospectively. The prevalence of MSSA and MRSA increased from 2010 to 2016, however, there was no statistically significant difference in the prevalence of *P. aeruginosa* over the years. There was a significant relationship between the development of antibiotic resistance and acute pulmonary exacerbations, pulmonary examination findings, loss in weight and height percentile. As the antibiotic resistance increased, PFT results were significantly decreased.

The most common microorganisms in CF at all ages are *S. aureus*, *P. aeruginosa*, *Nontuberculous Mycobacteria*, *S. maltophilia, A. xylosoxidans*, and *B. cepacia* complex (4). When we evaluated the distribution of microorganisms isolated from respiratory tract samples in our present study, *S. aureus* (MSSA+MRSA) was observed in 36.6%, followed by *P. aeruginosa* in 24.7%, *M. catarrhalis* in 9.2%, *S. pneumoniae* in 8.4%, *H. influenzae* in 7.4%, and MRSA in 5.6% of the cultures. Consistent with existing literature, our study found *S. aureus* and *P. aeruginosa* to be the most frequently isolated microorganisms in CF patients. In our study, 56% of patients had *P. aeruginosa* isolated from at least one culture. When the whole 333 cultures were evaluated, *P. aeruginosa* was isolated from 97 (24.7%) and MDR-*P. aeruginosa* from 48 (12.2%) cultures. However, our study found no changes in the prevalence of *P. aeruginosa* and MDR-*P. aeruginosa* from 2010 to 2016. In the recent Cystic Fibrosis Foundation's report, the prevalence of *P. aeruginosa* and MDR-*P. aeruginosa* was reported as 26% and 3.3%, respectively. The prevalence of *P. aeruginosa* decreased from 47.5% to 26% and MDR-*P. aeruginosa* decreased from 26% to 3.3%, from 2015 to 2022 (4). This decline may be due to fewer culture surveillances during the COVID-19 pandemic, increased use of highly effective modulator therapies, and enhanced infection prevention and control strategies.

A meta-analysis published in 2022 indicated that antibiotic resistance in CF patients, particularly against *P. aeruginosa* and *S. aureus*, poses a significant challenge in the long-term management of the disease. Furthermore, a gradual decline in antibiotic susceptibility has been demonstrated, further complicating treatment strategies (6,7). Susceptibility rates of *P. aeruginosa* for colistin were 95%, ceftazidime 73%, cefepime 60%, cefaperazone-sulbactam 56%, tobramycin 76%, levofloxacin 52%, ciprofloxacin 66%, and meropenem 71%, whereas susceptibility to piperacillin-tazobactam was shown to be 63% (6). When we compared our results with those reported in the meta-analysis, we found that the susceptibility rates of *P. aeruginosa* were similar for colistin (95%) and piperacillin-tazobactam (62%), but higher for ceftazidime (91%), cefaperazone-sulbactam (90%), cefepime (90%), tobramycin (88%), levofloxacin (84%),

Table 3. PFT results according to the drug resistance

	Non-R Cultures	SDR Cultures	MDR Cultures	p
FEV_1 (%)	89.9±19.6	69.8±16.9	59.0±22.5	**<0.001**[a,b]
FVC (%)	86.6±20.0	66.3±17.2	63.6±19.7	**0.003**[a,b]
FEV_1/FVC	102.5±10.1	103.6±4.0	90.0±12.4	**<0.001**[b,c]
PEF (%)	87.6±19.5	68.1±13.9	75.4±17.2	**0.002**[a]
FEF_{25-75} (%)	83.2±31.8	69.3±15.9	46.5±28.1	**0.001**[b]

PFT: pulmonary function test, Non-R: non-resistant, SDR: single-drug-resistant, MDR: multi-drug-resistant, FEV: forced expiratory volume, FVC: forced vital capacity, PEF: peak expiratory flow, FEF: forced expiratory flow, [a,b,c]: a significant difference between [a]: Non-R and SDR, [b]: Non-R and MDR, [c]: SDR and MDR cultures

ciprofloxacin (83%), and meropenem (81%). These findings indicate that antibiotic resistance has become a significant problem. The high rate of antibiotic use in the general population in Türkiye may have increased the resistance rates in the present study.

In CF patients, the prevalence of *S. aureus* showed an increase until the year 2020, followed by a decline. In 2015, the prevalence of *S. aureus* was 70.6% (44.6% MSSA, 26% MRSA), whereas in 2022, it was reported as 60.8% (45.2% MSSA, 15.6% MRSA). From 2002 to 2019, the prevalence of MRSA increased from 9.2% to 24.6%, while from 2019 to 2022, the prevalence of MRSA decreased from 24.6% to 15.6% (4). Consistent with the literature, an increase in the prevalence of *S. aureus* and MRSA was observed between 2010 and 2017. However, the decrease in the frequency of *S. aureus*, MSSA, and MRSA between 2019 and 2022 could be attributed to fewer culture surveillances during the COVID-19 pandemic, increased use of highly effective modulator therapies, and enhanced infection prevention and control strategies.

In a meta-analysis published in 2024, antibiotic resistance rates for MRSA in CF patients were reported as follows: erythromycin 84%, clindamycin 74%, fluoroquinolones 75%, rifampin 21%, tetracycline 31%, gentamicin 23%, and linezolid 3.4%. No MRSA strains resistant to vancomycin were observed (7). In our study, MRSA antibiotic resistance rates were: erythromycin 70%, clindamycin 36%, tetracycline 20%, gentamicin 21%, and trimethoprim-sulfamethoxazole 5%, indicating variations in drug resistance. Vancomycin, fluoroquinolones, and linezolid-resistant MRSA strains were not observed. However, recent literature shows an increase in antibiotic resistance over the years.

The early and accurate antibiotic treatment of the chronic *P. aeruginosa* and MRSA colonization in CF patients has been demonstrated to reduce lung damage and increase life expectancy. In addition to intravenous administration, alternative inhalation routes for antibiotics have been explored, yielding successful outcomes (16). Patients, especially those colonized with *P. aeruginosa*, may require long-term inhalation antibiotic therapy (17). In our study, no significant relationship was found between antibiotic resistance and the use of long-term inhaled antibiotics in the last 6 months, in the last 1 year, and at any period of life before culture. No relationship was observed between colonization and the development of antibiotic resistance.

Newborn screening for CF has been widely adopted worldwide. CF patients not diagnosed through the CF screening program might have worse respiratory functions, higher rates of chronic *P. aeruginosa* colonization, and more hospitalizations due to respiratory diseases (18). In our study, 15% of the patients were diagnosed through the newborn CF screening program. Although the number of patients diagnosed through the newborn screening program was low, we observed a higher rate of antibiotic resistance in respiratory tract specimens of patients diagnosed through the CF screening program compared to those not diagnosed through the program. Additionally, when we compared the age at the diagnosis of CF with microbial drug resistance, it was observed that as the age at diagnosis decreased, the development of resistance increased. These may be due to the fact that patients diagnosed through the screening program were monitored more closely, with an increased number of cultures being obtained during follow-up and an increased use of antibiotics.

Acute pulmonary exacerbations can occur in the clinical course of most CF patients, leading to deterioration in lung function. Antibiotic therapy should be initiated in the presence of acute pulmonary exacerbations (19,20). In our study, it was observed that the presence of auscultatory findings such as crackles and wheezing during physical examination at the time of culture collection was associated with increased antibiotic resistance. Additionally, the cultures obtained during periods of acute pulmonary exacerbation showed higher rates of antibiotic resistance. These suggest the necessity of obtaining cultures when there are signs of acute pulmonary exacerbation and adjusting antibiotic therapy according to the culture results.

A Cochrane review on the azithromycin treatment for anti-inflammatory purposes has shown that it improves lung function and increases FEV_1 in CF patients. It also reduces the frequency of acute pulmonary exacerbations. Furthermore, the use of azithromycin is associated with a decrease in the prevalence of *S. aureus* in cultures. There was no evidence in the review suggesting that azithromycin treatment increases the risk of MRSA compared to placebo (21). However, our study found a higher prevalence of *S. aureus* colonization in those using azithromycin compared to non-users, whereas, consistent with the literature, we did not observe a significant association between the long-term use of azithromycin and an increase in MRSA colonization. Furthermore, in our study, no significant association was found between the long-term use of azithromycin for 6 months before culture, within the past year, or at any time in life and the development of antibiotic resistance.

In CF patients, growth retardation and malnutrition are common issues. The nutritional status in these patients also affects lung function. Pediatric CF patients infected with MDR bacteria have lower BMI and lower FEV_1/FVC compared to those without MDR bacteria. In our study, when we evaluated the relationship between the development of antibiotic resistance and the decrease in patients' weight and height percentiles, a significant decrease in weight and height percentiles was observed as resistance increased (5).

In CF patients, spirometry is highly valuable in determining the severity of the disease and predicting prognosis (22). When we compared antibiotic resistance with spirometry results, a significant decrease was observed in FEV_1, FVC, FEV_1/FVC, PEF, and FEF_{25-75} values as antibiotic resistance increased. This indicates a negative impact of resistant microorganisms on the respiratory function test results of CF patients.

This study has several limitations that need to be recognized. Since it has been a single-center study, the findings might not be generalized to diverse CF populations. The relatively small sample size of CF patients and the limited number of cultures analyzed may affect the generalizability of the results. Some regression analyses could not be performed due to insufficient sample size. According to the literature and reference we used, all MRSA isolates are considered MDR due to

resistance to a key antimicrobial agent. This may have led to an overestimation of the MDR-MRSA burden. In addition, none of the patients in this study used modulator therapy, and the use of highly effective modulator therapies in the years after the completion of the study may affect the results. Therefore, current microbial trends in CF patients after the widespread use of highly effective modulator therapies may differ from those reported in this study.

CONCLUSION

Antibiotic resistance, especially MDR, is a significant issue in CF. In this study, MRSA prevalence increased over the years. As antibiotic resistance increases, loss in height and weight percentiles, and negative effects on respiratory function tests can be observed. It has been observed that antibiotic resistance is higher when there are signs of acute pulmonary exacerbation and auscultation findings such as crackles and wheezing. Therefore, it is important to obtain respiratory tract cultures regularly in CF patients and initiate rational antibiotic treatment (correct antibiotic, correct route, correct and effective dose, correct duration) based on culture results, especially when there are signs of acute pulmonary exacerbation.

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