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Original Article

Clinical findings of methicillin-resistant *Staphylococcus aureus* in cystic fibrosis

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ABSTRACT

Background. Methicillin-resistant *Staphylococcus aureus* (MRSA) rates have increased in cystic fibrosis (CF) patients.This study aimed to determine the rate of MRSA, define risk factors, and clarify the effect of MRSA on pulmonary functions, annual pulmonary exacerbation (aPEx) in children with MRSA positive CF.

Methods. This was a retrospective case control study. CF patients who had ≥1 MRSA (+) respiratory culture between September 2016-2019 were included. MRSA growth rate, colonization status, clinical characteristics, hospitalization rates, FEV1 %predicted, and z-score one year prior to the MRSA isolation, at MRSA growth and one year after MRSA growth were recorded. The aPEx rate changes before-after MRSA growth were evaluated.

Results. Sixty-one subjects who had ≥1MRSA growth and 66 controls were enrolled. There was no statistically significant difference between the spirometry indices at first, and 12th month after MRSA acquisition. The mean aPEx was 0.6 one year prior to MRSA acquisition and this rate significantly increased to 1.2 one year after MRSA growth($p<0.05$). The mean hospitalization rate before and after one year of MRSA acquisition significantly increased from 0.17(±0.12) to 0.48 (±0.3)(p:0.008) admissions per year.

Conclusions. MRSA growth was related to increased aPEx. Increased aPEx and hospitalization rates after MRSA acquisition suggest MRSA should be eradicated when detected.

Key words: cystic fibrosis, methicillin resistant *Staphylococcus aureus*, pulmonary exacerbation, colonization, treatment.

Pulmonary involvement is the major cause of morbidity and mortality in cystic fibrosis (CF). Methicillin-resistant *Staphylococcus aureus* (MRSA) is the third most common microorganism detected in CF lungs in the USA.[1] Persistent MRSA infection contributes to CF morbidity and mortality by accelerating pulmonary function decline, impairing lung function recovery after pulmonary exacerbations and requiring increased antibiotic therapies and in some cases hospitalizations.[2-8]

The aim of this study was to determine the frequency of MRSA detection in patients with CF and describe the clinical characteristics, risk factors and clarify the effect of MRSA on pulmonary function, body mass index (BMI) and annual pulmonary exacerbation (aPEx) in children with MRSA acquisition and chronic MRSA compared to methicillin-susceptible *Staphylococcus aureus* (MSSA) positive patients. The second aim of this study was to determine the effect of chronic MRSA colonization on the long-term outcome parameters.

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Material and Methods

Patients

This was a retrospective case-control study. Patients between 0-18 years with confirmed CF diagnosis who had MRSA growth in sputum or deep oropharyngeal cultures between September 2016 and June 2019 were enrolled. The study was approved by our local Hacettepe University Ethics Committee (15/09/2021, GO20-639). A control group was recruited from the same pool of CF patients with methicillin-susceptible Staphylococcus aureus (MSSA), and matched with each MRSA patient for gender age, *Pseudomonas aeruginosa* (PA) colonization, other comorbidities related to CF, and CF medications.

Patients' demographic data including age, sex, body mass index (BMI) z-score, age at CF diagnosis, CF mutations, presence of other pathogens, pulmonary function measured at baseline, and related diseases such as pancreatic insufficiency, CF-related diabetes, concurrent allergic bronchopulmonary aspergillosis and inhaler treatments used, age at the time of MSSA and MRSA acquisition were recorded. BMI z-score and spirometry indices one year prior to MRSA, at the time of the MRSA acquisition, and 12 months after MRSA acquisition were recorded. Pulmonary exacerbation rates and hospitalization frequency before and 12 months after MRSA acquisition were calculated for all the patients and patients with chronic MRSA. Symptoms, physical examination findings, and microbiological status (PA, *B.cepacia, non-tuberculous mycobacteria* (NTM), *and Achromobacter*) at the time of the MRSA acquisition and at the 12-month visit were documented. Antibiotics used, route of administration, duration of therapy, and hospitalization status for initial MRSA growth were also recorded. The number of clinic visits, PA colonization status in the last twelve months before MRSA acquisition were evaluated.

Measurements

In our center, CF patients are routinely evaluated every three months. During these visits, airway samples are obtained from all CF patients, and for patients older than 5 years of age spirometry is performed.

All the samples of *S. aureus* isolates were subjected to cefoxitin disc diffusion testing using a 30 μg cefoxitin disc. The results were interpreted according to EUCAST guidelines. MRSA growth was defined if it was stated in the microbiologic culture report as phenotype resistant to cefoxitin. A new MRSA growth was defined as at least one positive respiratory tract (RT) culture in patients who were negative during the previous 12 months. The duration for the development of methicillin resistance was calculated as the period between the MSSA positive culture and the initial MRSA growth.

A child with an initial positive RT culture for MRSA who never grew MRSA again in the following twelve months was characterized as having one MRSA growth. Among these patients who received antibiotic treatment specific for MRSA and three negative respiratory samples for MRSA taken at least one week apart showed no MRSA growth following treatment were specified as MRSA eradicated. The success of the given antibiotic to eradicate MRSA was calculated by proportioning the patients whose MRSA was eradicated among all patients receiving the same eradication therapy. Patients who had ≥3 MRSA cultures in the past 6 months were defined as chronic MRSA colonization.[9] MRSA prevalence was calculated by dividing the number of MRSA positive cultures detected during the study period to the total number of RT cultures of CF patients obtained during the study period.

Spirometry test was performed with the Vyntus PC Spirometer (Carefusion; Höchberg, Germany) and in accordance with the American Thoracic Society and European Respiratory

Society (ATS/ERS) standards by the same certified spirometry technician.[10] Spirometry indices were analyzed using the reference values of Quanjer et al.[11] Spirometry curves were re-evaluated by a single senior pediatric pulmonologist following the recently published update of the ATS/ERS standardization of spirometry.

BMI-for-age z-scores were calculated using the World Health Organization (WHO) anthropometric calculator (AnthroPlus v.1.0.4) which is based on WHO Child Growth Standards and Growth Reference data. Acute pulmonary exacerbation was defined according to criteria described by Fuchs et al.[12]

Infection Control Policy

As of February 2019, strict infection control practices have been implemented in our clinic. A brochure has been prepared to inform patients from this day on. Patients are encouraged to put on surgical masks throughout their hospital stay. Hand disinfectants have been placed in the waiting room and in the examination rooms and patients are asked to use them. No other CF patient or family member is permitted to be in another child's area at any time. Doctors wash their hands and clean their stethoscopes between patients. Children colonized with MRSA, PA, *Burkholderia cepacia* and NTM attend the outpatient clinic on a different day then other CF patients. Between patient examinations desktops, chairs, surfaces are thoroughly cleaned.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0(SPSS Inc,Chicago,IL). To find a significant difference between 2 groups with a big effect size (cohen d=0,95), the minimum required sample size was estimated as 126 (α=0.05-1-β=0.80).[13] The Kolmogorov-Smirnov test was used to determine whether variables had a normal distribution. Patient characteristics and pulmonary function variables were presented by means (SD), median (IQR) or numbers and percentages of total, as appropriate. The Wilcoxon signed-rank test was used for comparing repeated measurements that were not normally distributed. Differences between group characteristics were assessed by independent samples T-test or Mann–Whitney test. Differences for dependent variables were assessed by paired sample T-test. Chi-square or Fisher exact test was used to analyze group differences for categorical variables. The difference for previous, initial and last FEV_1 values, and difference of these values in different groups (one growth and chronic MRSA) were calculated with the generalized linear model. P values <0.05 were considered statistically significant.

Results

During the study interval, a total of 2734 RT cultures of CF patients were examined. Eighty-eight subjects had at least one MRSA growth in which 44 of them had MRSA growth for the first time. The MRSA prevalence in CF patients in our center during the study interval was 11.8%. During the same time interval, the MRSA prevalence of our center was 18.5%.

Patient characteristics

A total of 360 CF patients were followed at our clinic between the years 2016-2019. We only enrolled 61 CF patients between 0-18 years of age and (17%) who had ≥1 MRSA growth. The control group consisted of 66 patients between 0-18 years of age with chronic MSSA growth. The demographic data of subjects and clinical findings at MRSA acquisition are summarized in Table I. The median follow-up time for patients after MRSA acquisition was 14 months (IQR:12-20). The median MRSA acquisition after the first MSSA positive culture was 42.6 months (IQR: 24.4-89.3).

Table I. Demographic characteristics of subjects at time of positive MRSA growth, and control group and clinical findings and treatment data of subjects at MRSA acquisition.

	Patients with positive MRSA growth	MSSA positive group	p
Patients, n	61	66	
Male/female	32/29	33/33	
Mean age at study enrollment yr (SD)	8.2 (3.9)	9.4 (4.3)	0.2
Mean age for first MRSA positive culture yr (SD)	8.2 (3.9)	n.a.	n.a.
Mean age for first MSSA positive culture yr (SD)	3.8 (3.5)	3.2 (3)	0.8
Mean culture frequency per year (SD)	2.6 (0.9)	2.7 (0.8)	0.9
Sample collection, n (%)			0.3
Deep oropharyngeal culture	25 (41)	21 (31.8)	
Sputum culture	36 (59)	45 (68.2)	
Chronic *Pseudomonas aeruginosa* colonization, n (%)	15 (24.6)	14 (21.2)	0.7
Chronic *Achromobacter* colonization, n (%)	1 (1.6)	-	n.a.
Genotype, n (%)			0.5
ΔF508/ΔF508	11 (18)	14 (21.5)	
ΔF508/other	10 (16.4)	15 (23.1)	
Other/other	40 (65.6)	37 (56.1)	
Pancreatic insufficiency, n (%)	58 (95.1)	61 (92.4)	0.5
Chronic liver disease, n (%)	17 (27.9)	13 (19.7)	0.3
Altered glucose tolerance/ CF related diabetes, n (%)	6 (9.8)	3 (4.5)	0.3
Allergic bronchopulmonary aspergillosis, n (%)	1 (1.6)	2 (3)	0.6
Inhaled Medications, n (%)			
Dornase-alpha	57 (93.4)	66 (100)	0.2
Corticosteroids	4 (6.6)	4 (6.1)	0.9
Hypertonic saline	10 (16.4)	8 (12.1)	0.5
Mannitol	6 (9.8)	1 (1.5)	0.06
Tobramycin	12 (19.7)	10 (15.2)	0.5
Colistin	9 (14.8)	4 (6.1)	0.1
Clinical findings at MRSA acquisition		n.a.	n.a.
Symptomatic, n (%)	28 (45.9)		
Cough	28 (100)		
Increased sputum	8 (13.1)		
Fever	4 (6.6)		
Hypoxia	3 (4.9)		

IQR: interquartile range, SD: standard deviation, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-susceptible *Staphylococcus aureus*, n.a.: not applicable

Spirometry and BMI

Baseline and twelve month lung function, BMI, and frequency of pulmonary exacerbations of patients with MRSA acquisition and control group is shown in Table II. BMI z-score and spirometry indices of patients at initial MRSA growth, and 12 months after MRSA acquisition are summarized in Table III. There was no statistically significant difference between the first, and 12th month after MRSA acquisition in spirometry indices, whereas a significant increase was seen in BMI z-score at 12th month visit.

Table II. Baseline and twelve month lung function, body mass index and frequency of pulmonary exacerbations.

Characteristics		Control subjects	Patients	P value (case/ control)	One growth group	Intermitant/ Chronically infected group	P value (one growth/ inter-chronic)
Spirometry performed n (%)		48 (72.7)	41 (67.2)		10 (83.3)	32 (65.3)	
Baseline FEV1 z-score, mean (SD)		-0.41 (1.66)	-0.68 (2.00)	0.5	-0.67 (1.20)	-0.68 (1.10)	0.9
Twelve month FEV1 z-score, mean ± SD		-0.56 (1.85)	-0.91 (1.85)	0.4	-0.49 (0.74)	-1.04 (1.00)	0.2
Baseline FVC z-score, mean ± SD		-0.48 (1.49)	-0.78 (1.89)	0.4	-1.09 (1.52)	-0.68 (1.01)	0.5
Twelve month FVC z-score, mean ± SD		-0.57 (1.69)	-0.99 (1.70)	0.2	-0.53 (0.79)	-1.13 (1.17)	0.1
Baseline FEV1 %, mean ± SD		99.7 (18.9)	95.6 (23.4)	0.4	96.0 (21.2)	95.5 (21.3)	0.9
Twelve month FEV1 %, mean ± SD		97.3 (20.8)	94.5 (21.3)	0.5	100.3 (11.0)	92.7 (23.5)	0.2
Baseline FEV1 L median (IQR)		1.64 (1.35-2.32)	1.58 (1.18-2.10)	0.6	1.46 (1.18- 1.58)	1.81 (1.21-2.26)	0.2
Twelve month FEV1 L median (IQR)		1.71 (1.39-2.41)	1.81 (1.40-2.30)	0.9	1.68 (1.40-1.88)	1.93 (1.44-2.49)	0.4
Baseline FVC %, mean ±SD		95.1 (15.4)	91.3 (19.6)	0.3	89.1 (16.7)	91.9 (20.6)	0.7
Twelve month FVC %, mean ± SD		94.5 (16.4)	92.6 (18)	0.6	96.5 (10.7)	91.3 (19.7)	0.4
Baseline FVC L median (IQR)		1.83 (1.42-2.61)	1.88 (1.42-2.39)	0.8	1.50 (1.42- 1.78)	2.01 (1.36- 2.59)	0.1
Twelve month FVC L, median (IQR)		2.02 (1.58-2.80)	2.09 (1.62-2.72)	0.8	1.89 (1.69-2.10)	2.24 (1.59- 2.86)	0.3
Baseline BMI z score, mean ± SD		0.06 (1.30)	-0.05 (1.34)	0.6	0.01 (1.24)	-0.05 (1.30)	0.8
Twelve month BMI z score, mean ±SD		0.00 (1.35)	0.01 (1.36)	0.6	0.33 (1.10)	-0.08 (1.41)	0.3
Exacerbations	Year before baseline, mean (SD)	0.5 (0.1)	0.6 (0.1)	0.9	0.4 (0.1)	0.7 (0.1)	0.2
	Year after baseline, mean ±SD	0.5 (0.1)	1.2 (0.2)	<0.001	0.6 (0.1)	1.4 (0.1)	0.04*
Hospitalization	Year before baseline, mean ±SD	0.15 (0.01)	0.17 (0.02)	0.8	0 (0)	0.21 (0.01)	0.02*
	Year after baseline, mean ±SD	0.35 (0.07)	0.48 (0.03)	0.6	0.08 (0.03)	0.78 (0.10)	0.01*

BMI: body mass index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; IQR: interquartile range; SD: standard deviation; L: liter

Table III. BMI z-score and spirometric data of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) at the time of initial growth and twelfth month control.

	Initial	Twelfth month	p
Spirometry performed, n (%)	41 (67.2)	41 (67.2)	
FEV_1 % predicted mean (SD)	95.6 (23.4)	94.5 (21.3)	0.1
FVC % predicted mean (SD)	91.3 (19.6)	92.6 (18)	0.9
FEF_{25-75} % predicted mean (SD)	91.9 (37.7)	87.2 (32)	0.05
FEV_1 z-score mean (SD)	-0.68 (2.00)	-0.91 (1.85)	0.07
FVC z-score mean (SD)	-0.78 (1.89)	-0.99 (1.70)	0.2
FEF_{25-75} z-score mean (SD)	-0.73 (1.47)	-0.83 (1.73)	0.2
BMI z-score, mean (SD)	-0.05 (1.34)	0.01 (1.36)	0.001

Table IV. Treatment modalities given for patients with one MRSA growth and chronic MRSA, and eradication rates of the therapies.

	Patients with one MRSA growth n (%)	Patients with chronic MRSA n (%)	p
Received eradication therapy	7 (18.9)*	30 (81.1)	0.9
Eradication therapy route			
Intravenous	1 (10)	9 (90)	0.7
Oral	6 (22.2)	21 (77.8)	
Treatments			
TMP-SMX p.o., n (%)	5 (33.3)	10 (66.7)	0.5
TMP-SMX and rifampicin p.o.	1 (14.3)	6 (85.7)	n.a.
TMP-SMX and rifampicin p.o. + %2 nasal mupirosin ointment + %4 chlorhexidin BW	-	1 (100)	n.a.
Vancomycin iv.	1 (12.5)	7 (87.5)	n.a.
Linezolid iv.	-	2 (100)	n.a.
Other (p.o.)	-	4 (100)	n.a.

p.o: per oral, iv: intravenous , n.a: not applicable, TMP-SMX: Trimethoprim-sulfamethoxazole, BW: body wash
* The overall success rate for MRSA eradication was 18.9%.

aPEx and Hospitalization

The mean aPex was 0.6 one year prior to the MRSA acquisition and significantly increased to 1.2 one year after MRSA growth ($p<0.05$). The mean aPEX was significantly higher for patients one year after MRSA growth compared to the control group (1.2 versus 0.5; p: 0.001). The mean hospitalization rate before and one year after the MRSA acquisition significantly increased from 0.17 (±0.12) to 0.48 (±0.3) (p:0.008) admissions per year.

Treatment- Eradication- Chronic Colonization

Detailed antibiotic therapy regimes for 37 patients (60.7%) and eradication success are outlined in Table IV. MRSA was spontaneously cleared in 5 patients (8.2%) with only one MRSA growth without any medical treatment. When MRSA was detected for the first time, seven (58%) of the 12 patients with only one MRSA growth and 30 (61.2%) of the 49 patients with chronic MRSA colonization were treated with antibiotics which was not statistically significant (p:0.9). The overall success rate for MRSA eradication was 18.9%.

Results of patients with chronic MRSA

Among 49 patients the median MRSA colonization time was 17 months (IQR:10-29). Figure 1 shows the difference between median FEV_1 z-score values one year prior to MRSA, the initial MRSA growth and 12 months after MRSA acquisition compared for patients with and without chronic MRSA and the control group. Even though it was not statistically significant (p:0.08) the mean FEV_1 z-score one year prior to MRSA declined from -0.71 (±1.29) to -0.67(±1.20) at initial MRSA growth and increased to -0.49 (±0.74) at the one year follow up in patients with one MRSA growth, whereas FEV_1 z-score one year prior to MRSA declined from -0.31 (±1.64) to -0.68(± 1.10), and continued to decline to -1.04 (±1.00) at the one year follow up in patients with chronic MRSA.

Acute Pulmonary Exacerbations and Hospitalization

Among the patients who had one MRSA growth, the annual exacerbation rate before and after MRSA acquisition was found to be 0.4 and 0.6, respectively. This rate was 0.7 and 1.4 before and after the initial MRSA growth in patients who had chronic MRSA growth and this difference was statistically significant (p<0.05). None of the patients with one growth of MRSA were hospitalized after MRSA acquisition. However, the mean hospitalization rate was 0.2 in patients with chronic MRSA, but this difference was not statistically significant (p: 0.2).

Factors associated with chronic MRSA

Twelve patients had PA chronic colonization in the 12-month period prior to MRSA acquisition, 11 (91.7%) of them became chronically colonized with MRSA, whereas this rate was 77.3% in patients without chronic PA(p:0.2). All patients who came for routine follow up ≥3 times (n:5) during the 6-month interval before MRSA acquisition had chronic MRSA colonization, this rate decreased to 78.3% in patients who had visits 1-2 times (n:46) and to 66.7% in patients who did not come for follow up (n: 3) in the last 6 months (p:0.3). Data of eight patients could not be reached. Additionally, nine patients (14.5%) were hospitalized within 12 months before

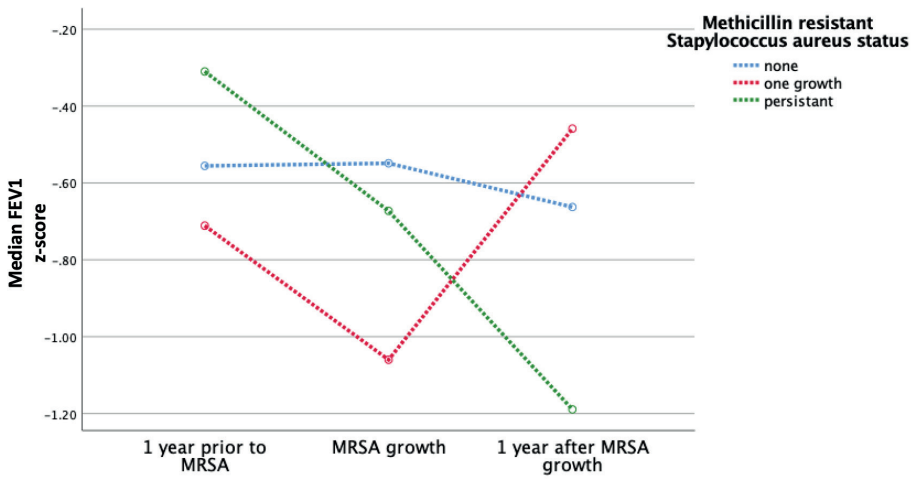

Fig. 1. Median FEV_1 z-score values one year prior to MRSA, the initial MRSA growth and 12 months after MRSA acquisition compared for patients with and without chronic MRSA and the control group. On Y-axis median FEV_1 score, on X-axis one year prior to MRSA, the initial MRSA growth and 12 months after MRSA acquisition is shown.

Table V. Logistic regression analysis for variables predicting chronic MRSA colonization.

Variables	Univariate analysis		
	Odds ratio	95% confidence interval	p
Age of encounter with MRSA	1.05	0.86-1.27	0.6
Chronic PA colonization in the 12-month prior to MRSA	0.3	0.03-2.7	0.3
Number of visits in the 6-month interval prior to MRSA	0.6	0.46-1.28	0.5
Hospitalization status in the 12-month interval prior to MRSA	0.7	0.56-1.33	0.7
Received treatment for MRSA	0.8	0.70-2.27	0.5

MRSA growth was detected. All of the patients who were hospitalized became chronically colonized with MRSA, whereas 76.7% were chronically colonized with MRSA in the non-hospitalized group (p:0.1). These factors were not found to have a significant effect on chronic colonization of MRSA in the regression analysis (Table V).

Discussion

In our study, we found that the MRSA prevalence in our center was 11.8%. Half of the patients were symptomatic and one-fourth had intermittent/persistent PA colonization when MRSA was detected for the first time. There was no significant decline in spirometry indices in the year following the MRSA acquisition, but a significant increase was found in the BMI z-score for the whole MRSA group. However, aPEx frequency one year after MRSA acquisition significantly increased compared to one year prior to the MRSA acquisition, this increase was also seen when compared with the control group. The overall success rate for MRSA eradication, and the rate of chronic MRSA in our cohort was 18.9% and 80% respectively. For the patients with chronic MRSA, the FEV1 z-score declined, and the aPEx rate increased compared to patients with one MRSA growth and the control group.

The prevalence of MRSA is reported in a wide range between countries and depends on many factors such as hospital policies for the management of MRSA, geographic differences and antibiotic susceptibility. MRSA prevalence increased from 9.2% to 25.9% between 2002 and 2017, even to 49% in some high prevalence centers in the USA.[14,15] A much lower prevalence is reported in European countries, Canada and Australia ranging between 3-18%.[9,16-19] A previous study from our center reported MRSA prevalence as 3.9% between 2003-2010.[20] The increase in MRSA prevalence in our center can be explained by several factors. First of all, the same patient population with increasing age is associated with an increased risk of antibiotic use, more frequent exacerbations and hospitalization, therefore an increase in MRSA prevalence. Besides strict infection control practices for CF were not implemented before January 2019. Therefore, children may have acquired MRSA in the clinic or hospital before that time.

Optimal treatment strategies for the eradication treatment of MRSA in patients with CF is debatable as well as the duration of the therapy and using monotherapies or combination therapies.[21-26] The treatment decision covering all of these aspects are mostly made on an individual basis combined with the patient's medical history and microbiologic test results. A recent Cochrane review concluded that due to lack of randomized controlled long-term trials, no recommendations can be made to support the eradication of MRSA, or a treatment protocol for MRSA.[27] In our study, 60% of the patients were treated when MRSA was detected for the first time yet 80% of the patients developed chronic MRSA. The success rate of MRSA eradication depends on the prevalence of MRSA in the community. It

may be successful if the household members/ community are not colonized with MRSA. However, we could not define the household members' MRSA colonization status and as such, we did not recommend any treatments to other household members for MRSA when MRSA treatment was initiated to the MRSA positive CF patients. Vallières et al.[21] examined 38 CF patients with MRSA, in their study nine different treatment modalities were used and they had an eradication success of 79%. More than one-half of the patients received a combination of rifampicin and fusidic acid treatment. This combination was not used in our study for two reasons. First of all, fusidic acid preparation is not available in our country and secondly, most patients have had difficulty attaining rifampicin which is a main anti-tuberculosis drug that can only be obtained from tuberculosis dispensaries in our country and is of limited use due to the concerns about the development of drug resistant tuberculosis. The higher rate of chronic MRSA than most of the other studies can be explained by several factors. Mainly, in the study group half of the patients were asymptomatic which caused less frequent eradication treatment for MRSA. Vallières et al.[21] treated most of the patients for at least 3 weeks and some of the patients for up to 6 months with additional nasal and skin decolonization protocol for all the patients. Even though they showed no difference in terms of eradication in patients with a longer duration of therapy, in our study the duration of the treatment was 14 days which is much lower, and only 1.6% of the patients in our study received decolonization protocol. All of these findings suggest that the combination of systemic and topical treatment strategies might enhance MRSA eradication and therefore reduce MRSA chronicity.

The rate of FEV_1 decline is still the most important outcome measure to monitor morbidity and mortality in CF. There was no statistically significant difference in terms of first and last spirometry indices, in our group. Similarly, Sawicki et al.[2] stated that MRSA detection was not associated with a significant decline in spirometry indices. On the other hand, Dasenbrook et al.[4] showed FEV_1 decline to increase in patients between 8-21 years who had chronic MRSA. Also, Vanderhelst et al.[5] reported an increased rate of decline in FEV_1. However, Sawicki et al.[2] included patients who had one positive culture for MRSA like our study, whereas the other two studies only included patients who had at least 3 cultures positive for MRSA. These findings raise the question of whether chronic MRSA state is related to FEV_1 decline in CF patients. In our study FEV_1 declined by 6% in patients with chronic MRSA, however, this decline didn't reach statistical significance. Yet the latter studies monitored their patients for 3.5-6 years, which is longer than that of the current study's follow-up period. These findings suggest that these patients in the study group should be followed closely and carefully for a significant decline in FEV_1 in the near future.

Our study has several limitations; the retrospective nature and small sample size, as well as the shorter follow up time can alter the results. Additionally, molecular analyses on the MRSA strains were not performed. The detection of MRSA carrier status of people living in the same house as the CF patient was also not obtained which may have helped to evaluate possible patient-to-patient transmission or other sources of contamination. We additionally were unable to interpret the small colony variant *S.aureus* status of our patients which is correlated with lung function decline and antibiotic resistance in CF patients.

Colonization with MRSA is an important problem for CF patients. Prevalence and chronicity rates differ between CF centers because of the lack of standardized protocols for eradication and treatment of intermittent and persistent MRSA. In our study, the increased prevalence of MRSA in CF patients, as well as chronic MRSA rates, is a warning for all the authors that strict infection control practices for CF are required, which have been implemented since January 2019. Also, even though FEV_1

decline could not be proven the increased pulmonary exacerbation and hospitalization rates after MRSA acquisition suggest that MRSA should be eradicated when detected. The failure of the MRSA eradication treatment suggests that a combination of systemic and topical treatment strategies might enhance MRSA eradication and chronicity. However larger prospective longitudinal studies are needed to focus on the benefits of eradication treatment of CF prognosis, duration of treatment, method of providing the treatment and the potential negative impacts of long-term treatments.

Ethical approval

Participation informed consent was involved and the study was approved by Hacettepe University ethics committee (GO20-639).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BÖ, DD, NE, GH, EY, UÖ, NK; data collection: BÖ, DAT, BS, HNB, İG; analysis and interpretation of results: BÖ, DD, EY, UÖ, NK; draft manuscript preparation: BÖ, DD, NE, GH. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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