Comparison of Intravenous and Non-Intravenous Antibiotic Regimens in Eradication of P. aeruginosa and MRSA in Cystic Fibrosis

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Abstract

Background: Chronic pulmonary infection is the leading cause of mortality and morbidity in patients with cystic fibrosis (CF). The most common pathogens isolated in CF are Staphylococcus aureus and Pseudomonas aeruginosa (P. aeruginosa). Chronic infection of P. aeruginosa and MRSA are associated with worse survival and antibiotic eradication treatment is recommended for both. This study evaluates the efficacy of intravenous (IV) vs. non-IV antibiotics in the eradication of P. aeruginosa and MRSA. Methods: This was a single-center retrospective study at a large CF center. All respiratory specimen cultures of 309 CF patients and eradication regimens between 2015-2019 were reviewed. The primary analysis was the comparison of the percentage of successful eradication after receiving IV and non-IV eradication regimens. Demographic and clinical risk factors for eradication failure were also analyzed. Results: 102 patients with P. aeruginosa isolations and 48 patients with MRSA were analyzed. At one year, 21.6% in P. aeruginosa group and 35.4% in MRSA group were successfully eradicated. There was not any statistically significant difference between IV vs. non-IV antibiotic regimens on eradication in either group. Additionally, none of the clinical risk factors was significantly associated with eradication failure in P. aeruginosa and MRSA groups. Conclusion: In the eradication of P. aeruginosa and MRSA, IV and non-IV treatment regimens did not show any superiority to one another. Non-parenteral eradication could be a better option in eradication considering the cost-effectiveness and the treatment burden of IV treatments due to hospitalization and the need for IV access.

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Abstract

Background: Chronic pulmonary infection is the leading cause of mortality and morbidity in patients with cystic fibrosis (CF). The most common pathogens isolated in CF are *Staphylococcus aureus* and *Pseudomonas aeruginosa* (*P. aeruginosa*). Chronic infection of *P. aeruginosa* and MRSA are associated with worse survival and antibiotic eradication treatment is recommended for both. This study evaluates the efficacy of intravenous (IV) vs. non-IV antibiotics in the eradication of *P. aeruginosa* and MRSA.

Methods: This was a single-center retrospective study at a large CF center. All respiratory specimen cultures of 309 CF patients and eradication regimens between 2015-2019 were reviewed. The primary analysis was the comparison of the percentage of successful eradication after receiving IV and non-IV eradication regimens. Demographic and clinical risk factors for eradication failure were also analyzed.

Results: 102 patients with *P. aeruginosa* isolations and 48 patients with MRSA were analyzed. At one year, 21.6% in *P. aeruginosa* group and 35.4% in MRSA group were successfully eradicated. There was not any statistically significant difference between IV vs. non-IV antibiotic regimens on eradication in either group. Additionally, none of the clinical risk factors was significantly associated with eradication failure in P. aeruginosa and MRSA groups.

Conclusion: In the eradication of *P. aeruginosa* and MRSA, IV and non-IV treatment regimens did not show any superiority to one another. Non-parenteral eradication could be a better option in eradication considering the cost-effectiveness and the treatment burden of IV treatments due to hospitalization and the need for IV access.

Keywords: Cystic fibrosis, Pseudomonas Aeruginosa, MRSA, eradication, antibiotic, chronic infection

Abbreviations

CF: Cystic Fibrosis

CFTR: Cystic fibrosis transmembrane conductance regulator

TORPEDO-CF: Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis

Introduction

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease in Caucasian populations. Thickened mucous secretion caused by the mutations on the CFTR gene leads to obstruction in the bronchioles secondary to mucus plugging. This causes an optimal environment for bacterial growth and infection[1]. Chronic pulmonary infection damaging the lung parenchyma and decreasing the pulmonary function is the leading cause of mortality and morbidity in individuals with CF [2-4]. The most common microorganisms isolated from respiratory secretions in CF are *Staphylococcus aureus (S. aureus)* and *Pseudomonas aeruginosa (P. aeruginosa)*[4].

Chronic infection of *P. aeruginosa* is associated with more parenchymal damage, a more rapid decline in lung function, and earlier mortality [2; 5]. The acquisition of *Methicillin-resistant S. aureus* (MRSA), even though that is not seen as much as *P. aeruginosa* , causes a decline in forced expiratory volume in 1-second percent predicted ($FEV1_{pp}$) and associated with worse survival[6; 7]. Current guidelines recommend antibiotic eradication treatment for MRSA and *P. aeruginosa* to prevent lung damage and chronic infections[8; 9].

The antibiotic eradication treatment for *P. aeruginosa* and MRSA is an established standard of care worldwide[9-13]. However, the most effective route of administration of antibiotics (oral, inhalation or intravenous (IV)) and choice of antibiotic regimen are not clear. The two Cochrane reviews on this matter state that there is still insufficient data to decide on which antibiotic strategy should be used for the eradication of early *P. aeruginosa* or MRSA in CF[14; 15].

There are numerous randomized controlled trials (RCT) on comparing different oral antibiotic regimens, oral vs. inhalation regimens and oral/inhalation combination regimens for *P. aeruginosa* eradication [14]. While there are many retrospective studies comparing inhalation and oral antibiotic regimens, there are only two RCTs for MRSA eradication[15]. On the other hand, there are few studies comparing IV vs. oral/inhalation antibiotic regimens. To date, there is only one RCT comparing IV and non-parenteral antibiotics for the eradication of *P. aeruginosa* and there have been no published data that investigate the efficacy of IV compared to non-parenteral antibiotics to eradicate MRSA[16].

Today, many CF clinics use IV antibiotics as antibiotic eradication treatment. IV eradication regimen requires hospital admission, IV access which might be traumatic and may worsen patient's health-related quality of life (HRQoL) [17]. Additionally, IV eradication regimens increase health-care costs significantly [16]. In this study, we investigate the efficacy of IV vs. non-IV (oral and/or inhalation) antibiotic eradication treatments for the eradication of the first isolation of *P. aeruginosa* and MRSA in individuals with CF. Additionally, we aim to determine clinical variables associated with chronic infection of *P. aeruginosa* and MRSA.

Materials and Methods

This was a single-center retrospective study conducted at the Marmara University Medical Faculty Selim Çöremen CF Center between January 2015 and December 2019. 309 patients with CF were involved in the study. The inclusion criteria were: CF diagnosis according to the consensus guidelines from the Cystic Fibrosis Foundation[18], regular follow-up in the CF center outpatient clinic and having at least 4 sputum or deep pharyngeal swab cultures per year (every 2-4 months).

All sputum and deep pharyngeal swab cultures collected from subjects between 2015-2019 were reviewed. Patients who had their first isolation of *P. aeruginosa* or MRSA were grouped separately. Patients' demographics, anthropometric measurements, clinical findings, chest physiotherapy (CPT) techniques, regular treatments and eradication regimens were obtained from the medical records.

Chronic or intermittent infection of *P. aeruginosa* or MRSA were determined according to the Leeds Criteria[19]. The Leeds Criteria defines chronic infection as having positive *P. aeruginosa* or MRSA in more than 50% of the cultures in the preceding year and intermittent infection as having positive *P. aeruginosa*

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or MRSA in less than 50%. Successful eradication was set as not having any isolation of *P. aeruginosa* or MRSA during 12 months after having the eradication regimen for their first isolation. Patients were followed up at least one year after their first isolation of *P. aeruginosa* or MRSA.

The primary analysis of the study was the comparison of the percentage of successful eradication after receiving IV and non-IV (oral and/or inhalation) eradication regimens. Sex, diagnosis age, age at isolation, body mass index (BMI) z-score, [?]F508 mutation, pancreatic insufficiency, CF-related Diabetes Mellitus (CFRD), biliary-hepatic disease, azithromycin use, dornase-alfa use, inhaled corticosteroid use, allergic bronchopulmonary aspergillosis (ABPA), previous *methicillin-sensitive S. aureus* (MSSA), chest physiotherapy and FEV1pp were analyzed as predictors of eradication failure.

The aim of the study was explained and informed consent was obtained from the participants beforehand. The Marmara University Medical Faculty Research Ethics Committee had approved the study with protocol number 09.2020.509.

Hospital eradication protocol

All patients with the first isolation of *P. aeruginosa* and MRSA were offered IV antibiotic eradication treatment. 14 days IV ceftazidime and amikacin were used for *P. aeruginosa* eradication. For the eradication of MRSA, 14 days IV teicoplanin was used in addition to 5 days 2% nasal mupirocin ointment and 5 days 4% chlorhexidine body wash. The regimens were adapted if a patient had any allergies or was resistant to any of the first-line antibiotics. If a patient did not accept hospitalization, an oral and/or inhalation eradication regimen was chosen by specialist decision.

Collection and processing of Respiratory Tract Samples

Respiratory samples taken from CF patients including sputum and deep pharyngeal swab samples (DPS) collected with ESwab (Copan Diagnostics, Murrieta, CA) sent to the microbiology laboratory for processing and inoculation. An equal volume of Sputasol solution (Thermo Scientific, USA) was added to the sputum samples and homogenized in a shaker incubator for 1 hour at 37 degC. The samples were vortexed in every 15 minutes and the resulting homogenates were inoculated whereas DPS samples were processed directly. Samples were inoculated into Mac Conkey agar, 5% sheep-blood agar, *Haemophilus* selective agar (chocolate agar including bacitracin), *Burkholderia cepacia* selective agar (BCSA), CHROMID$^{(r)}$, *S.* aureus Elite agar (SAIDE) agar plates then incubated for 24-72 hours at 35.5 degC. All plates were purchased from bioMerieux. Culture media evaluated daily for significant bacterial growth and if colonies exist, identification of microorganisms done by Matrix-Assisted Laser Desorption/Ionization time-of-flight, Mass Spectrometry (MALDI-TOF MS, BioMerieux, France). Antimicrobial susceptibility testing has done by Kirby-Bauer disk diffusion method and Vitek 2 system (bioMerieux). Results were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Statistical Analysis

Continuous variables were presented as mean +- standard deviation (SD). Baseline patient characteristics and study outcomes were analyzed between IV and non-IV treatment arms in *P. aeruginosa* and MRSA groups separately. Continuous data were analyzed via independent-samples T test or Mann-Whitney U tests for non-parametric data. Categorical data were analyzed via χ2 or Fisher's exact tests. P-value [?] 0.05 was considered to be significant. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) Version 23.

Results

Demographics and medical data

A total of 309 CF patients were involved in the study. Of these 309 patients, 120 had their first isolation of *P. aeruginosa* and 61 had first isolation of MRSA during the study period (2015-2019). 18 patients from *P. aeruginosa* group and 13 patients from MRSA group were excluded from the study due to lack of medical records or delayed treatment due to the presentation to the clinic later than the first month of isolation.

Patients' baseline characteristics are presented in Table 1. Baseline characteristics were similar between IV and non-IV treatment arms except patients who had IV treatment in *P. aeruginosa* group were younger (aged 5.1 ± 4.9 vs 8.1 ± 5.8 p =0.02).

Pseudomonas Aeruginosa Group (N=102)

The mean age of the patients at first isolation of *P. aeruginosa* was 5.83 ± 5.28 years. The mean duration from diagnosis to first *P. aeruginosa* isolation was 4.16 ± 4.0 years. While 22 isolations (21.6%) from patients were successfully eradicated at 1 year after their first isolation, 56 (54.9%) had intermittent and 24 (23.5%) had chronic infection (Table 2).

The most common preferred eradication regimen in our clinic was intravenous amikacin and ceftazidime for 14 days. Table 2 shows the successful eradication rates by antibiotic regimens. The highest success rate among treatment regimens was 14 days ciprofloxacin PO + 28 days inhaled tobramycin by 62.5% vs. IV amikacin + ceftazidime by 20.3% but this difference was not statistically significant ($p > 0.05$). When IV amikacin + ceftazidime and other non-intravenous treatment regimens compared, there was not any statistically significant difference ($p = 0.54$). Results of antibiotic susceptibility testing showed 89.2% of isolations were sensitive to all antibiotics and 10.8% were resistant to one or more antibiotics. Patients received their eradication regimens according to the antibiotic susceptibility of their microbial cultures.

Sex, diagnosis age, age at isolation, BMI z-score, ΔF508 mutation, pancreatic insufficiency, CFRD, biliary-hepatic disease, dornase alfa use, inhaled corticosteroid use, ABPA, hospitalization in the preceding year and FEV_{1pp} were not statistically significant as a predictor ($p > 0.05$) .

26 out of 102 patients were able to perform spirometry. The mean FEV1pp of eradicated group (n = 6) was 81.6 ± 9.02 and not eradicated group (n = 20) was 91.8 ± 18.65. This difference was not statistically significant ($p > 0.05$).

Methicillin-Resistant Staphylococcus Aureus Group (N=48)

The mean age of the patients at first isolation of MRSA was 7.66 ± 5.71 years. The mean duration from diagnosis to first MRSA isolation was 6.3 ± 5.25 years. While 17 isolations (35.4%) were successfully eradicated at 1 year, 17 patients (35.4%) had intermittent and 14 (29.2%) had chronic infection (Table 2).

The most common MRSA eradication regimen used in our clinic was intravenous teicoplanin for 14 days. The highest success rate among treatments was 14 days oral Trimethoprim / Sulfamethoxazole (TMP/SMX) + Rifampicin by 50% eradication success. Statistical analysis did not show any difference between treatment regimens ($p > 0.05$). Additionally, successful eradication rates were not significantly different between intravenous and oral treatment groups ($p = 0.57$).

Sex, diagnosis age, age at isolation, BMI z-score, ΔF508 mutation, pancreatic insufficiency, CFRD, biliary-hepatic disease, dornase alfa use, inhaled corticosteroid use, ABPA, hospitalization rate in the preceding year and FEV1pp were not statistically significant as a predictor ($p > 0.05$).

20 out of 48 patients were able to perform spirometry. The mean FEV1pp of patients in eradicated and not eradicated groups were 88.9 ± 21 and 93.2 ± 13.1, respectively ($p > 0.05$).

Discussion

The present study was designed to evaluate the efficacy of IV antibiotics compared to non-IV eradication regimens. IV antibiotic treatment is considered to be more effective compared to other routes in pulmonary exacerbation and it is recommended for the patients with moderate to severe pulmonary exacerbation or with no response to oral and/or inhalation antibiotics[20]. There is a limited data on IV vs oral and/or inhalation antibiotic regimens for the eradication of early *P. aeruginosa* or MRSA acquisition. The data from our study demonstrated that there is not any statistically significant difference between IV vs non-IV (oral and/or inhalation) antibiotic eradication regimens in terms of eradication at one year of the first isolation of *P. aeruginosa* and MRSA.

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IV treatment often requires hospitalization, might have a negative effect on HRQoL in individuals with CF and costs significantly more than oral/inhalation treatments[16; 21]. Although a number of studies have been reported the effectiveness of oral, inhalation and IV eradication protocols, there are only a few comparative studies available and the optimal antibiotic regimens for both MRSA and *P. aeruginosa* are not clear. [12; 15; 22].

A recent RCT on *P. aeruginosa* eradication compared the efficacy of 14 days IV ceftazidime and tobramycin vs 12 weeks oral ciprofloxacin; both groups were combined with 12 weeks inhaled colistimethate sodium[16]. In line with our results, IV antibiotics did not achieve sustained eradication of *P. aeruginosa* in a greater proportion of patients with CF compared to the oral therapy group. The study also evaluated the cost-effectiveness and found that oral eradication therapy has similar effectiveness for the primary clinical parameters and considerably cheaper compared to IV treatment.

Even though non-parenteral eradication protocols have been more commonly used since they have similar effectiveness with IV treatment and more preferable method in terms of cost effectiveness and patients QoL, insufficient effect of inhaled antibiotics on inflammation is a valid concern. A RCT comparing the systemic antibiotics to inhaled tobramycin alone in terms of reduction in lower airways inflammation suggests that systemic antibiotic treatment has a greater effect on reducing lower airways inflammation, even though systemic and inhaled treatments appeared to have similar effects on reduction of bacterial burden[23]. These results might cause concerns about the impact of inflammation in lower airways such as increase in bronchiectasis and decrease in pulmonary function. However, studies did not show any difference in $FEV1_{pp}$ change between inhaled with oral antibiotics and only inhaled antibiotic regimens [24; 25].

There are several MRSA eradication protocols evaluated in the literature including very mild regimens such as single or dual oral antibiotics and very aggressive treatments such as dual iv antibiotic treatment over 3 weeks followed by a 6-week period with dual oral antibiotic therapy and inhalation with vancomycin, all in addition to environmental hygienic directives and topical therapies[22; 26-31]. These studies have been reported successful eradication rates from 41.4% to 84% with the first isolation for MRSA. The successful eradication rate of MRSA in our study cohort was 35.4%. Our eradication rate was lower than other studies and this might be due to the different study end-points. We determined the successful eradication as not having any isolations 12 months after the treatment compared to evaluating at 28-day of the treatment in most of the studies in the literature.

To the best of our knowledge, this is the first study comparing IV and non-IV antibiotics for the eradication of MRSA. Our results indicate that oral antibiotics (TMP/SMX with or without rifampicin) may be as efficient as IV teicoplanin for the eradication treatment.

Determining risk factors influencing acquisition and eradication of MRSA and *P. aeruginosa* in CF is crucial for prevention and treatment success. To date, studies showed lower socio-economic status, female gender, ΔF508 mutation and pancreatic insufficiency as risk factors for *P. aeruginosa* [32; 33]. Additionally, retrospective cohort studies of individuals with CF in the Cystic Fibrosis Foundation Patient Registry demonstrated that pancreatic insufficiency, CFRD and number of hospitalizations in the preceding year were the most common risk factors for eradication failure of MRSA[34; 35]. In our study, none of these clinical risk factors were significantly associated with eradication failure both in *P. aeruginosa* and MRSA groups.

Our study has a number of limitations. Firstly, this is a retrospective design and the generalizability of the results is limited due to being a single-center study. Also, while our sample size is relatively bigger than comparative studies in the literature, most patients were given IV treatment due to the hospital protocol and this limited the numbers of non-IV treatment cohort.

In conclusion, we did not find any difference between IV and non-IV treatments in successful eradication at 1 year for both *P. aeruginosa* and MRSA. This study, in line with TORPEDO-CF, shows that IV treatment does not add any benefit in the eradication of *P. aeruginosa* [16]. Additionally, eradication rates were not significantly different in the eradication of MRSA and this should be verified by further prospective studies. In light of these results, cost-effectiveness and to decrease the treatment burden due to hospitalization and

IV administration of antibiotics, we have increased the use non-parenteral eradication protocols in our CF clinic.

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Conflict of interest

None declared.

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