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Not a wild goose chase: Long-lasting MRSA negative status following eradication therapy for chronic MRSA infection in patients with cystic fibrosis

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Abstract

Objectives. Prevalence of MRSA in patients with CF has risen over the past decades, and chronic infection with MRSA is associated with worse outcome in this patient group.

Methods. This retrospective observational study investigated long-term eradication rate in pediatric and adult CF patients with chronic MRSA infection, using a 6-month eradication regimen containing 2 oral antibiotics, combined with topical decolonisation measures. Respiratory tract cultures were performed at least every three months, from the first MRSA-positive culture onwards.

Results. A total of 24 patients with chronic MRSA infection were identified from our CF patient registry, of which 13 patients underwent an eradication attempt. The regimen consisted of 2 oral antibiotics: a combination of rifampicin, fusidic acid, clindamycin and co-trimoxazol, based on the sensitivity pattern of the MRSA strain. At the end of the study period (median 8.2 years), 12 out of 13 patients (92%) were MRSA negative. None of the patients interrupted treatment due to side-effects.

Conclusions. Eradication of chronic MRSA infection is feasible, well-tolerated and highly successful, and can offer a long-lasting MRSA-negative status, obviating the need for patient segregation.

Introduction

Improvements in care have led to prolonged survival of cystic fibrosis (CF) patients over the past decades. However, pulmonary infections and colonization with resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as a new challenge, with prevalence ranging from 5.9% (in 2019 in Belgium) (1) up to 24.6% (in 2019 in the US) (2). Cross-sectional and longitudinal studies have shown an association between (chronic) MRSA infection and worse clinical outcome, although results are inconsistent (3,4,5). Furthermore, it remains unclear whether MRSA is simply a marker of more severe lung disease or an independent contributor to lung function decline (6). Aside from possible somatic implications of MRSA in CF, patients with MRSA may also suffer a psychological impact from segregation measures (7) or experience worse quality of care (8), as these measures are more strict than for patients colonized with for instance *Pseudomonas aeruginosa* (9).

Several small clinical trials investigated different eradication strategies for - mostly newly acquired - MRSA (8,10,11,12). Only two of these were randomized controlled trials, both examining patients with first or early MRSA infection. Muhlebach et al used an eradication regimen consisting of oral co-trimoxazole and rifampicin for 2 weeks, combined with topical and environmental decontamination (13). Dolce et al used the same antibiotic combination, during 3 weeks, without topical or environmental decontamination (14). The control arm was observation only in both trials. They both showed successful eradication after 28 days and 6 months, respectively. However, in the trial by Muhlebach et al, by day 168 there was no difference in the proportion of participants who remained MRSA-negative in either treatment arm. This was also the case in the trial by Dolce et al, after 6 months of

follow-up. As such, until date there is no consensus as to the optimal eradication regimen (10). Moreover, none of these trials studied long-term (>6 months) microbiological outcome after eradication. Hence, the objective of this study was to investigate long-term eradication rate in pediatric and adult CF patients with chronic MRSA infection, using an eradication regimen containing 2 oral antibiotics, combined with topical decolonisation measures.

Methods

We conducted a retrospective observational study at the CF reference centre of the Brussels University Hospital, using data from January 1997 until December 2020 (ethics committee approval BUN 143201938573). All CF patients with chronic MRSA infection who underwent an eradication attempt were included. Chronic MRSA infection was defined as having at least 3 respiratory tract cultures positive for MRSA during a period of 6 months. Respiratory tract cultures were performed at least every three months, from the first MRSA-positive culture onwards, until the end of the study period or until lung transplant, death or loss to follow-up. MRSA clearance was defined as the absence of MRSA in at least three cultures over a period of 6 months. We also collected baseline clinical characteristics from the patients' electronic medical file.

Results

A total of 24 patients with chronic MRSA infection were identified from our CF patient registry, of which 13 patients underwent an eradication attempt. The remaining 11 patients did not undergo an eradication attempt due to unstable clinical status, chronic liver disease or patient refusal of additional treatment burden. Table 1 summarizes the clinical characteristics of the study population at time of first MRSA-positive culture. Eleven of these patients underwent an eradication attempt in the context of a clinical trial (BUN 143201213745). This was a prospective observational trial, conducted at the same CF centre from 2011 until 2013, aiming to examine the feasibility, tolerance and efficacy of MRSA eradication, using a 6-month regimen of a combination of 2 oral antibiotics, together with topical decolonization measures (15). The 2 other patients underwent an eradication attempt later on, after the end of the inclusion period of the prospective trial. Six patients received a combination of rifampicin 15 mg/kg and fusidic acid 30 mg/kg daily, 4 patients received a combination of rifampicin and clindamycin 25 mg/kg daily, 2 patients were treated with rifampicin and co-trimoxazol 8 mg/kg daily (trimethoprim component), and 1 with clindamycin and co-trimoxazol, based on the sensitivity pattern of the strain. Topical decolonisation measures consisted of mupirocin-containing nasal ointment 3 times daily, and chlorhexidine hair and body wash once daily, both during 5 days.

Median follow-up time of respiratory tract cultures after first MRSA-positive culture was 10.2 (IQR: 9.4-13.2) years. Median time from first MRSA-positive culture to start of eradication was 1.0 (IQR: 0.7-4.6) year. All but 2 patients (85%) had a negative respiratory culture for MRSA at the end of the eradication scheme, which was maintained 3 and 6 months later (Table 2). These 2 patients did eventually also clear MRSA (without

supplementary intentional eradication treatment) at 0.6 and 3.2 years after the end of eradication therapy. Of the patients who had been successfully eradicated during the eradication protocol, two suffered recurrence, 2 and 3.8 years after the end of eradication therapy respectively. These patients underwent a repeat eradication attempt within 3 months after recurrence, consisting of rifampicin and fusidic acid, and of vancomycin followed by linezolid, respectively, which was successful in 1 of the 2 patients. At the end of the study period (median 8.2 (IQR:7.9-8.7) years), 12 out of 13 patients (92%) were still MRSA negative. These data are schematically displayed in Figure 1. None of the patients interrupted treatment due to side-effects.

Eleven patients didn't undergo an eradication attempt due to unstable clinical status, chronic liver disease or patient refusal of additional treatment burden. Their median follow-up time of respiratory tract cultures was 13.4 (IQR: 7.8-17.0) years after first MRSA-positive culture. Only one patient in this group was MRSA negative 6 months after first positive culture. At 5 and 10 years after first positive culture, respectively 6 out of 10 (60%) and 4 out of 8 patients (50%) were still chronically infected with MRSA. Of note, this group can by no means be considered a matched control group for the patient group that did undergo an eradication attempt, as these are patients of older age, with worse FEV_1, worse clinical status and co-morbidities such as chronic liver disease.

Discussion

Our data show that eradication of chronic MRSA infection using a 6-month course of 2 oral antibiotics (usually including rifampicin) associated with topical decolonisation measures is feasible, safe and successful, even after a long follow-up period. Treatment was well-tolerated, and none of the patients failed to fully complete the treatment regimen, showing that this fully oral treatment protocol is easy to use. A limit of the eradication scheme can be the limited availability of oral fusidic acid (for example in the U.S.), and the possible interaction with medication such as ivacaftor, a component of all currently approved CFTR modulator therapies.

Our study group consisted of patients with chronic and also longstanding MRSA infection, and most of these patients remained MRSA negative for almost a decade after eradication. Indeed, 92% of our eradicated patients were still MRSA negative at a median follow-up time of 8.2 years after eradication therapy. To the best of our knowledge, this is the first study examining such long-term eradication rate of chronic MRSA infection. Considering that patients with chronic (as opposed to transient) MRSA infection show a more rapid decline in FEV_1 (4,16), and that newly acquired MRSA infection is transient in almost half of patients with MRSA (16), we advocate this eradication protocol only in patients with chronic MRSA infection, to minimize treatment burden and possible side effects.

Few trials have explored MRSA eradication in patients with chronic MRSA infection (11,15,17,18) and it appears that monotherapy lacks effectiveness and that a short treatment duration results in early recurrence of MRSA. Indeed, only the 2 trials examining a combination of 2 oral antibiotics (including rifampicin) during a prolonged treatment period

of 6 months, together with topical decolonisation measures, were able to obtain successful eradication at 6 months after the end of treatment (15,18). These two trials reported few side effects (mostly gastro-intestinal) in 3 out of 7 patients (18) and in 5 out of 11 patients (15), which led to early treatment cessation in only one patient (18). It is important to note that topical decolonisation may also be necessary to improve eradication rate, as eradication failure has been shown to be associated with cutaneous colonisation (19). When considering an eradication attempt, systemic and topical treatment should be combined to optimize MRSA clearance, as was done in the studied group, which likely contributed to the high eradication success rate. Of note, we cannot exclude the possibility that, during the follow-up period, these patients may have been treated with antibiotics potentially active against MRSA for other purposes such as co-infection with other pathogens – a limitation inherent to the retrospective design of this study.

Two patients suffered recurrence of MRSA infection after an initial successful eradication. The MRSA strain in both patients showed the same sensitivity pattern as the strain before eradication, suggesting that prolonged eradication treatment had not induced resistance to the antibiotics used.

The limitations of our study include the retrospective design of the study, the small sample size inherent to the study subject, and the lack of a control group, limiting the generalizability of our results. This is also why we did not include here clinical outcomes nor evolution of lung function, as these could be influenced by a number of other confounding factors (such as colonisation with other micro-organisms, development of CFRD, adherence to therapy, and CFTR-modulator treatment), especially given the long follow-up period and inherent bias from different treatment eras. Also, we have no data from molecular strain

typing of MRSA strains, which could have helped to evaluate whether eradication holds a risk of inducing resistance to the antibiotics used.

In conclusion, our data show that eradication of chronic MRSA infection in CF patients using a 6-month course of 2 oral antibiotics (usually a combination with rifampicin and adapted to the sensitivity pattern of the MRSA strain) combined with topical decolonisation measures, is feasible, well-tolerated and highly successful, even in patients with long-standing MRSA infection. Our eradication regimen provided a long-lasting MRSA-negative status in all but 1 patient, obviating the need for segregation of these patients. However, to minimize treatment burden, we advocate to eradicate only when chronic MRSA infection is present. Our findings should be confirmed in prospective studies, also focusing on the impact of MRSA eradication on clinical outcome.

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Table 1. Clinical characteristics of the study population and eradication regimens.

	Study population (n = 13)
Sex: M	7 (54%)
Age (years)	8.0 (5.4-16.2)
Body mass index (kg/m^2)	15.9 (14.8-19.3)
Homozygous for F508del	7 (54%)
FEV$_1$ (%P)	86 (84-104) ([1])
Bronchiectasis	11 (85%)
Chronic co-infection with *Pseudomonas aeruginosa*	4 (31%)
Hospitalization in the year preceding first MRSA-positive culture	10 (77%)
Pancreatic insufficiency	12 (92%)
CFRD	2 (15%)
Eradication regimens:	
Rifampicin + fusidic acid	6 (46%)
Rifampicin + clindamycin	4 (31%)
Rifampicin + co-trimoxazole	2 (15%)
Clindamycin + co-trimoxazole	1 (8%)

Data are presented as median (IQR) for continuous variables. For categorical variables, the number of observations and percentages are given in each category. All data described are at first MRSA-positive culture. ([1]) Two patients were too young to perform spirometry at first MRSA-positive culture. Abbreviations: M: male sex; MRSA: methicillin-resistant *Staphylococcus aureus*; CFRD: cystic fibrosis related diabetes; FEV_1: forced expiratory volume in 1 second.

Table 2. Microbiological data of the study group undergoing eradication

	Study population (n = 13)
Follow-up time from MRSA positivity (years)	10.2 (9.4-13.2)
Time from MRSA positivity to eradication (years)	1.0 (0.7-4.6)
MRSA negative	
At end of treatment	11 (85%)
3 months after end of treatment	11 (85%)
6 months after end of treatment	11 (85%)
5 years after end of treatment	12 (92%)
End of study ([1])	12 (92%)

Data are presented as median (IQR) for continuous variables. For categorical variables, the number of observations and percentages are given in each category. Abbreviations: MRSA: methicillin-resistant *Staphylococcus aureus*. [(1)] End of study corresponded to a median of 8.2 (IQR: 7.9-8.7) years after end of eradication treatment.

Figure 1. Schematic display of the microbiological data