ORIGINAL ARTICLE

Microbiological efficacy of early MRSA treatment in cystic fibrosis in a randomised controlled trial

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ABSTRACT

Objective To evaluate microbiological effectiveness, that is, culture negativity of a non-blinded eradication protocol (Rx) compared with observation (Obs) in clinically stable cystic fibrosis participants with newly positive methicillin resistant Staphylococcus aureus (MRSA) cultures.

Design This non-blinded trial randomised participants ages 4–45 years with first or early (≤2 positive cultures within 3 years) MRSA-positive culture without MRSA-active antibiotics within 4 weeks 1:1 to Rx or Obs. The Rx protocol was: oral trimethoprim-sulfamethoxazole or if sulfa-allergic, minocycline plus oral rifampin; chlorhexidine mouthwash for 2 weeks; nasal mupirocin and chlorhexidine body wipes for 5 days and environmental decontamination for 21 days. The primary end point was MRSA culture status at day 28.

Results Between 1 April 2011 to September 2014, 45 participants (44% female, mean age 11.5 years) were randomised (24 Rx, 21 Obs). At day 28, 82% (n=18/22) of participants in the Rx arm compared with 26% (n=5/19) in the Obs arm were MRSA-negative. Adjusted for interim monitoring, this difference was 52% (95% CI 23% to 80%, p<0.001). Limiting analyses to participants who were MRSA-positive at the screening visit, 67% (8/12) in the Rx arm and 13% (2/15) in the Obs arm were MRSA-negative at day 28, adjusted difference: 49% (95% CI 22% to 71%, p<0.001). Fifty-four per cent in the Rx arm compared with 10% participants in the Obs arm remained MRSA-negative through day 84. Mild gastrointestinal and skin related side effects were higher in the Rx arm.

Conclusions This MRSA eradication protocol for newly acquired MRSA demonstrated microbiological efficacy with a large treatment effect.

Trial registration number NCT01349192.

INTRODUCTION

Infection with methicillin-resistant Staphylococcus aureus (MRSA) continues to have a significant impact in hospital and community acquired infections.1–3 In subjects with cystic fibrosis (CF) the prevalence of MRSA-positive respiratory cultures increased from 11.9% in 2003 to 25.6% in 2013 in US CF-centres and contributes to adverse outcomes in CF.3–4 Cross-sectional, epidemiological studies demonstrated that MRSA was associated with lower lung function in CF3,4 and greater use of medical therapies.7 Longitudinal outcomes of MRSA in CF have noted differing results; one study found no difference in lung function decline whereas another study showed greater lung function decline in those acquiring persistent MRSA infection.8,9 Similarly, patients with CF with persistent MRSA infection may have increased mortality.10 Treatment approaches highlighted by case series have varied widely from observation to long-term or intravenous antibiotics with the goal of eradicating MRSA.11–13 Despite the evolving concern of this organism in the CF community, to date there are no randomised studies demonstrating if treating MRSA at initial detection can eradicate MRSA and prevent chronic respiratory infection. Despite MRSA rates being significantly lower than in the USA, many European countries treat any positive respiratory cultures of MRSA and Methicillin susceptible Staphylococcus aureus (MSSA); alternatively, US guidelines do not recommend treatment of incident MRSA or MSSA in CF.3 The risks of indiscriminate and prolonged treatment of MRSA acquisition include the emergence of new/increasingly resistant organisms and treatment related toxicity.

The current study aimed to evaluate the 28-day safety and microbiological efficacy, that is, microbiological treatment effect, of an MRSA eradication

Key messages

What is the key question?

- Is aggressive treatment of incident methicillin-resistant Staphylococcus aureus (MRSA)-positive respiratory culture in cystic fibrosis effective at reducing MRSA culture positivity and is it clinically safe?

What is the bottom line?

- This multifaceted oral, topical and environmental treatment protocol demonstrated a strong microbiological treatment effect in children and adults with few treatment related side effects, which were mostly gastrointestinal and skin related.

Why read on?

- To learn about the duration of MRSA-negative cultures and secondary outcomes, that showed favourable trends despite a small sample size.
protocol in patients with CF with newly acquired MRSA as compared with observation alone. We hypothesised that patients with CF who are clinically stable at time of first detection of MRSA in a respiratory culture are more likely to be MRSA culture-negative following an intense multifaceted eradication protocol compared with the current US standard of care of not treating MRSA when patients are stable.

**MATERIALS AND METHODS**

**Study centres**

The trial was conducted from 1 April 2011 to September 2014 at 14 CF foundation accredited care centres in the USA. The trial was coordinated by the CF Foundation Therapeutics Development Network Coordinating Center (Seattle, Washington, USA) and registered on clinicaltrials.gov (NCT01349192).

**Study participants**

Eligibility criteria included a confirmed diagnosis of CF, age 4–45 years at time of consent and a new onset MRSA-positive culture from sputum, or oropharyngeal (OP) swab or bronchoscopy. New onset was defined as an MRSA-positive culture within 6 months that was either the first lifetime MRSA-positive culture or new emergence of MRSA after at least 1 year of documented negative cultures (minimum of two cultures/year while off MRSA active antibiotics) for MRSA in participants with up to two MRSA-positive cultures in the past 3.5 years. After the planned interim review the Data Monitoring Committee (DMC) recommended that the number of study sites be increased and that subjects MRSA-negative at screening visit be included if the initial clinical MRSA isolate was available. This was to enhance enrolment and to reflect clinical practice. Participants had to be clinically stable within the 14 days prior to screening. Exclusion criteria included having received antibiotics with activity against MRSA or use of an investigational drug within 28 days of screening, and FEV₁ <30% of predicted based on reference equations.**14 15 Participants with contraindications for study medications, that is, allergy or renal or hepatic dysfunction were not eligible. Microbiological contraindications were resistance of the available MRSA isolate to trimethoprim-sulfamethoxazole (TMP-SMX) and minocycline or rifampin.

**Randomisation and blinding**

Participants were randomised (1:1) to an MRSA eradication protocol as outlined below or to no treatment within strata defined by site, age (4–12 years, 13–45 years) and presence of *Pseudomonas aeruginosa* at screening. Randomisation assignments were generated via a centralised, secure web based randomisation system for each enrolled subject. Study personnel and participants were not blinded to the treatment regimen.

**Treatment regimen (Rx)**

The treatment protocol for those randomised to the MRSA eradication protocol consisted of two oral antibiotics for 2 weeks combined with nasal, skin and oral decontamination as well as 3 weeks enhanced household cleaning. Study medications were oral TMP-SMX dosed as per CF guidelines at 8 mg/kg TMP/40 mg/kg SMX for children <40 kg and 320 mg/1600 mg for adults, given twice daily for 14 days. In participants intolerant to TMP-SMX, minocycline, if >8 years, at a dose of 100 mg twice daily was substituted. All participants randomised to the treatment protocol received combination therapy with rifampin (15 mg/kg/day up to 40 kg or 300 mg twice daily). Nasal mupirocin and whole body cleansing with chlorhexidine wipes were used for 5 days in addition to twice daily gargling with 0.12% chlorhexidine gluconate oral rinse for 14 days. Enhanced household cleaning included weekly washing of linens and towels, wiping down high contact surfaces, for example, toys and computers with chlorhexidine, and extra cleaning of airway clearance devices. Selection of the Rx regimen was based on decolonisation strategies in non-CF populations and TMP-SMX was selected based on a US observational trial of CF which had shown that most MRSA isolates were susceptible to TMP-SMX and rifampin, with very low resistance rates to mupirocin.**16 17**

For participants randomised to the observation (Obs) arm, treatment with anti-MRSA therapy prior to day 28 was only allowed for a protocol defined exacerbation with choice of antibiotics as per the participant’s treating physician. Use of anti-MRSA antibiotics after day 28 was allowed for both arms.

**Clinical evaluations**

Medical history, physical examination, specimen sampling for microbiology (OP nasal, groin and axilla swabs on all participants, additional sputum in those expectorating) and spirometry were obtained at the screening visit (day 14). Clinical evaluations, physical examination and spirometry were performed on day 1 (randomisation), day 15, day 28, day 84 and day 168. Follow-up after day 28 was used to assess durability of treatment effect. Pulmonary function testing was performed in accordance with American Thoracic Society standards.**18** Adverse events and concomitant medications were recorded during each visit and by phone calls conducted on day 7. Protocol defined pulmonary exacerbations were defined using a combination of spirometry, X-ray and clinical symptoms as in prior studies.**19**

**Primary and secondary outcomes**

The primary outcome of the study was difference in the proportion of MRSA-negative subjects based on OP-swab or sputum on day 28 between the two study arms. Secondary end points included safety, tolerability of the treatment regimen, protocol adherence, duration of microbiological effect, number of pulmonary exacerbations, use of antibiotics, change in spirometry (as measured by FEV₁), respiratory symptoms as measured by the CF-specific patient outcomes: Cystic Fibrosis Questionnaire Revised respiratory domain scores and Cystic Fibrosis Respiratory Symptom Diary Chronic Respiratory Infection Symptom Scale, and weight.

**Statistical analysis**

The study design specified randomisation of 90 participants providing 80% power to detect a difference of 30% or greater in the proportion of respiratory cultures negative for MRSA at day 28 (Rx minus Obs). The sample size calculations assumed a dropout rate of 10%, ensuring 40 randomised participants to Rx and 40 to Obs arms.

Safety outcomes were monitored throughout the trial by a DMC appointed by the CF Foundation Safety Monitoring Board. One interim analysis with early stopping for futility was scheduled to take place after approximately half of the participants had been randomised into the study and had completed the day 28 visit. Because of slow accrual, an early interim review and futility analysis of the primary end point was initiated when 24 participants had completed the first 28 days of the study. Upon review of the interim results, the DMC recommended continuance of the study with a second interim analysis for early efficacy. The study team remained blinded to findings presented to the DMC. Statistical ramifications of this
Figure 1 CONSORT diagram of participant disposition. Flow diagram of participants through each stage of the randomised trial. (1) Nine participants did not meet the inclusion criteria of being clinically stable. One of these participants was subsequently re-screened but failed the inclusion criteria of methicillin-resistant Staphylococcus aureus (MRSA)-positive culture at screening or within 6 months prior to screening. Eleven participants failed the inclusion criteria of MRSA-positive culture at screening or within 6 months prior to screening. One participant did not meet the inclusion criteria by withdrawing their consent. One participant did not meet the inclusion criteria of having a documented cystic fibrosis (CF) diagnosis. Two participants met the exclusion criteria of receiving anti-MRSA antibiotics within 28 days prior to screening. One participant met the exclusion criteria that warranted a screen failure due to investigator’s opinion. (2) Two participants randomised to the observational control arm withdrew with reason ‘Subject decision’. (3) The intent-to-treat (ITT) population is defined as participants who are randomised to a study arm and followed post randomisation. The ITT population is used for all safety and secondary efficacy analyses. (4) One site, which enrolled a total of four participants (two in the treatment arm, two in the observational control arm), experienced numerous study conduct issues and protocol violations resulting in missing primary end point and other end point data. One of these four participants had withdrawn immediately following randomisation to the observational control arm. The remaining three participants’ data are summarised as available post randomisation. (5) The ITT-efficacy (ITT-E) population consists of all the participants in the ITT population who were assessed for the primary microbiological efficacy end point at baseline and day 28. The ITT-E population is used for the primary efficacy analyses. (6) The per-protocol-efficacy (PPE) population is comprised of all participants in the ITT-E population excluding the participants with major protocol violation or those non-compliant with oral antibiotic use during the first 28 days of the study. The PP population is used in sensitivity analyses of primary efficacy end point. TMP-SMX, trimethoprim-sulfamethoxazole. BL, baseline; PP, per protocol.
unplanned efficacy analysis are addressed in the online supplemental material.

All of the safety and secondary efficacy analyses were conducted on the intent-to-treat (ITT) population. The primary efficacy analyses were performed on the ITT-efficacy (ITT-E) population. The per-protocol-efficacy (PPE) population was used in sensitivity analyses of the primary end point. The detailed definitions of analyses populations are provided in figure 1. T-tests were used to compare continuous variables by study arm. The comparisons of proportions were performed using Fisher’s exact test, with corresponding 95% CI derived using the Newcombe-Wilson method. Event rate comparisons were performed using Poisson regression. In the analyses of the primary end point, the difference in the proportion of respiratory cultures negative for MRSA at day 28 (Rx minus Obs), the treatment effect, 95% CIs and p value estimates were adjusted for the interim reviews. The use of group sequential stopping rules alters the sampling distribution of the usual fixed sample statistics and so adjustments need to be made to compute the point estimates, CIs and p values. The results of final analyses had to be adjusted for bias to account for multiple looks at the data during the two interim reviews (referred to as ‘adj. for interim monitoring’).

p Values and CIs are two-sided with 0.05 significance level; analyses were performed using SAS (V9.4, SAS Institute, Cary, North Carolina, USA, 2013) and R (V3.2.1, The R Foundation for Statistical Computing, Vienna, Austria, 2015).

RESULTS

Although the planned sample size was 90 patients, the DMC recommended that the enrolment of new participants be stopped early with ongoing follow-up of enrolled subjects, after interim review by the DMC showed a statistically significant microbiological treatment effect. At the time the trial was stopped, 73 participants had been screened at 14 participating centres; 45/73 participants were randomised and followed post-randomisation (ITT population), 24 in the Rx and 21 in the Obs arms (figure 1).

Clinical characteristics of the ITT participants (n=45) showed a mean age of 11.5 years with well-preserved lung function (table 1). The two arms were comparable at baseline (table 1) and distribution of participants who had a sputum sample in addition to OP swab did not differ by study arm (no participant included based on bronchoscopy results). Of the 45 randomised participants, 41 (22 Rx and 19 Obs) were included in the ITT-E analyses. Although the protocol allowed changing from TMP-SMX to minocycline in case of side effects, none changed treatment during the study; however, two subjects in the Rx arm were started on minocycline due to previously known intolerances to TMP-SMX. A total of seven participants withdrew post randomisation (three (13%) in Rx and four (19%) in Obs); four withdrew before day 28 visit and were not assessed for the primary microbiological end point (figure 1).

Table 2 summarises the primary end point, that is, changes in MRSA culture status from screening through day 28. Those who were not positive at screening had a confirmed MRSA isolate at a clinic visit within a median of 46 days (range 14–154 days) prior to screening. The proportion of participants in the ITT-E population who were MRSA-negative at day 28 was 82% (n=18/22) in the Rx arm compared with 26% (n=5/19) in the Obs arm. Adjusted for the interim reviews, the difference in the proportion being MRSA-negative at day 28 (Rx minus Obs) was 52% (95% CI 23% to 80%, p<0.001). In a sensitivity analysis limited to participants who were MRSA-positive at the screening visit, 67% in the Rx compared with 13% in the Obs arm were MRSA-negative at day 28, with an adjusted difference of 49% (95% CI 22% to 71%, p<0.001). These results prompted the DMC to recommend early study closure (see online supplementary material labelled Statistical Monitoring Guidelines and Interim Primary End point Analyses).

Online supplementary table S1 shows results of sensitivity analyses within the first 28 days for the primary efficacy end point. These sensitivity analyses addressed the use of anti-MRSA antibiotics within the first 28 days. For all of the sensitivity analyses, the inference was consistent with the primary analysis and in particular, the observed treatment effect was stronger in the PPE population.

In the ITT population, 15 participants (65%) were compliant for Statistical Computing, Vienna, Austria, 2015).

Table 1 Demographics and baseline characteristics by study arm

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=24)</th>
<th>Observational control (n=21)</th>
<th>Total (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex—<strong>female</strong></td>
<td>10 (42)</td>
<td>10 (48)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>19 (79)</td>
<td>17 (81)</td>
<td>36 (80)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (13)</td>
<td>2 (10)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>African-American</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F508 del homozgyous</td>
<td>6 (25)</td>
<td>12 (57)</td>
<td>18 (40)</td>
</tr>
<tr>
<td>F508 del heterozygous</td>
<td>14 (58)</td>
<td>7 (33)</td>
<td>21 (47)</td>
</tr>
<tr>
<td>Other*</td>
<td>4 (17)</td>
<td>2 (10)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–12</td>
<td>13 (54)</td>
<td>15 (71)</td>
<td>28 (62)</td>
</tr>
<tr>
<td>&gt;12–18</td>
<td>6 (25)</td>
<td>5 (24)</td>
<td>11 (24)</td>
</tr>
<tr>
<td>&gt;18</td>
<td>5 (21)</td>
<td>1 (5)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa-positive</td>
<td>4 (17)</td>
<td>4 (19)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>FEV1% predicted group*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–50% predicted</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>&gt;50–75% predicted</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (3)</td>
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<tr>
<td>&gt;75–100% predicted</td>
<td>7 (35)</td>
<td>5 (29)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>&gt;100% predicted</td>
<td>11 (55)</td>
<td>12 (71)</td>
<td>23 (62)</td>
</tr>
</tbody>
</table>

This table summarises demographic and baseline characteristics by study arm in the ITT population. All measures were recorded at screening.

*Other refers to participants with either two known, non-delta F508 CF mutations, or one known, non-F508 del CF mutation and one unidentified allele which has not been classified as a CF mutation.

†For participants 6 years or older, FEV1% predicted is calculated based on the Wang (boys <18 years, girls <16 years) or Hankinson (boys >18 years, girls >16 years) reference equations. Percentages are based on number of participants with FEV1 measurements available (20 in the treatment arm and 17 in the observational control arm).

†The centiles are derived using CDC standards for participants ≤20 years old. CF, cystic fibrosis; ITT, intent-to-treat.
protocol was acceptable to patients and families with a relatively low treatment burden (see online supplementary material). Adherence with environmental decontamination was very good with two participants (9%) reporting missing ≥5 days of wipes and one participant missing ≥1 time of washing the linens. There were three instances of oral antibiotic discontinuation due to adverse events ‘probably related’ to study drug: two were temporary discontinuation of rifampin due to gastrointestinal (GI) complaints, whereas one participant had to discontinue all antibiotics due to urticaria. None of the adverse events was considered serious or required hospitalisation. Unrelated to adverse events one participant discontinued rifampin early and one participant reported taking TMP/SMX only once daily.

Two serious adverse events occurred during the first 28 days on study, one in the Rx arm (increased cough) and one in the Obs arm (cellulitis of the eyelid). Types of adverse events were more likely related to gastrointestinal and skin/subcutaneous tissue disorders in the treatment arm. No significant laboratory related adverse events were identified (see online supplementary table S2 and Safety Laboratory Assessment). There were no microbiological adverse events (ie, no emergent MRSA resistances to antibiotics used or appearance of small colony variants).

Use of anti-MRSA antibiotics is shown by individual participants in figure 2 from screening through day 168 by study arm together with MRSA culture status. After day 28, nine (38%) participants in the Rx and nine (43%) in the Obs arm were treated with anti-MRSA antibiotics. The usage of non-MRSA active acute oral, inhaled or intravenous antibiotic was comparable between treatment arms during the first 28 days as well as throughout the study. Participant-specific MRSA culture results show that 13 of 24 participants (54%) in the Rx arm were MRSA-negative at day 28 and remained negative through day 84 (figure 2A) as compared with two of 21 (10%) participants in the Obs arm (figure 2B). The impact of acute antibiotic administration in the Obs arm on the treatment effect is examined in online supplementary tables S3.1 and S3.2.

Two participants, one in each arm, were hospitalised during the first 28 days of the study. Over the entire course of the study, two (8%) participants in the Rx arm were hospitalised 3 times and five (24%) were hospitalised in the Obs arm 11 times (difference = −15%, 95% CI −38% to 6%, p=0.22). The rate of hospitalisation from screening through day 168 was significantly lower in the Rx arm versus the Obs arm (RR=0.22, 95% CI 0.05 to 0.72, p=0.01).

The proportion of participants experiencing at least one pulmonary exacerbation between screening and day 28 (calculated as the proportion of patients experiencing an event per 28 days of follow-up) was 13% in the Rx arm as compared with 33% in the Obs arm (95% CI −44% to 4%, p=0.15). Similarly, the rate of exacerbation from screening through day 28 was lower in the Rx arm versus the Obs arm, (RR=0.36, 95% CI 0.08 to 1.29, p=0.12), although not statistically significant.

Table 2 Microbiological effect at day 28

<table>
<thead>
<tr>
<th>Treatment (N=24)</th>
<th>Observational control (N=21)</th>
<th>Difference (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number screened</td>
<td>24</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>MRSA-positive at screening, n (%)</td>
<td>14 (58%)</td>
<td>17 (81%)</td>
<td>−23% (−45% to 4%)*</td>
</tr>
<tr>
<td>Day 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number completed</td>
<td>22</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>MRSA-negative at day 28, n (%)</td>
<td>18 (82%)</td>
<td>5 (26%)</td>
<td>52% (23% to 80%)‡</td>
</tr>
<tr>
<td>Change from screening to day 28</td>
<td>12</td>
<td>15</td>
<td>49% (22% to 71%)‡</td>
</tr>
</tbody>
</table>

This table summarises analysis of primary end point, that is, proportion of participants in the ITT-E population with an MRSA-negative culture at day 28, adjusted for interim review. Also summarised is the proportion of MRSA-negative cultures at day 28 among participants with an MRSA-positive culture at screening. For participants that have both an OP and expectorated sputum sample available at a given visit, a positive respiratory culture result is based on MRSA being present in either the OP or expectorated sputum sample; a negative result is based on MRSA being absent from both the OP and expectorated sputum samples.

*95% CI calculated using the Newcombe-Wilson method without continuity correction.
†The p value is obtained from Fisher’s exact test.
‡Adjusted for the interim reviews.
§Number of participants with both an MRSA-positive respiratory culture result available at screening, and a non-missing MRSA culture result at day 28.
¶Per cent value is based on the number of participants with an MRSA-positive respiratory culture result available at screening.


The p value is obtained from Fisher’s exact test.

This figure shows that 13 of 24 participants (54%) in the Rx arm were hospitalised during the first 28 days of the study. Over the entire course of the study, two (8%) participants in the Rx arm were hospitalised 3 times and five (24%) were hospitalised in the Obs arm 11 times (difference = −15%, 95% CI −38% to 6%, p=0.22). The rate of hospitalisation from screening through day 168 was significantly lower in the Rx arm versus the Obs arm (RR=0.22, 95% CI 0.05 to 0.72, p=0.01).

The proportion of participants experiencing at least one pulmonary exacerbation between screening and day 28 (calculated as the proportion of patients experiencing an event per 28 days of follow-up) was 13% in the Rx arm as compared with 33% in the Obs arm (95% CI −44% to 4%, p=0.15). Similarly, the rate of exacerbation from screening through day 28 was lower in the Rx arm versus the Obs arm, (RR=0.36, 95% CI 0.08 to 1.29, p=0.12), although not statistically significant.

At screening, 14 of 45 participants had nasal MRSA colonisation. The proportion colonised was similar in the two treatment arms: 6 of 24 (25%) in the Rx and 8 of 21 (38%) in the Obs (p=0.52) arms. No treatment related differences emerged. Only one patient was MRSA colonised at the skin (see online supplementary tables S4.1 and S4.2). Participants with persistent or re-emergent MRSA infection kept the same Staphylococcal chromosome cassette mec (SCCmec) type. There were no differences in proportion colonised with P. aeruginosa at screening, with 4 of 24 (17%) in the Rx and 4 of 21 (19%) in the Obs arms (p>0.999). No differences emerged during the course of the trial.

At day 28, the mean relative change in FEV1 (litres) from screening was 2.5% in the Rx arm (n=19) and −2.4% in the Obs arm (n=16) (difference = 4.9%, 95% CI −0.6% to 10.4%, p=0.08); the mean absolute change in FEV1 (% predicted) was 0.7% in the Rx arm and −4.1% in the Obs arm with a difference of 4.8%, 95% CI −0.9% to 10.5%, p=0.10. At day 168, the differences (Rx−Obs) in mean relative change in FEV1 (litres) were 3.1% (95% CI −2.5% to 8.6%, p=0.27) and the mean absolute change in FEV1 (% predicted), 4.7% (95% CI −0.4% to 9.8%, p=0.07) (see figure 3). Online supplementary figures S1.1 and S1.2 show the changes in FEV1 (litres) and FEV1 (% predicted).

There were no significant differences between study arms with respect to changes in weight or patient reported outcomes (see online supplementary figures S2.1, S2.2, S2.3, S3.1 and S3.2).
Prevalence of MRSA in CF is ∼26% in the USA and chronic infection has been associated with higher rates of lung function decline and mortality.91 The current randomised controlled trial evaluated a comprehensive protocol with two oral antibiotics for 2 weeks combined with nasal, skin and oral decontamination as well as a 3-week environmental decontamination in clinically stable patients with CF. This treatment led to a marked reduction in culture positivity (OP swab or sputum) at 28 days compared with the observational arm. The treatment
effect was large enough to recommend early study termination by the DMC due to evidence of microbiological efficacy, that is, the high rate or MRSA-negative cultures in the Rx compared with the Obs arm. Positive trends were also seen for secondary outcomes with reduction in the rate of pulmonary exacerbation and a trend towards improved lung function despite the study population having preserved lung function at baseline. As expected for these antibiotics, the rate of GI side effects was higher in the Rx arm, however the only permanent discontinuation of antibiotics was for urticaria. Thus, the treatment regimen appeared overall safe and, despite some drug related side effects, well tolerated. Despite most participants reporting that the regimen was acceptable, compliance with all aspects of this regimen was not ideal, which may be related to the multifaceted approach.

The possibility of treating MRSA successfully and achieving eradication even in settings of chronic infection has been reported.11–13 20–22 None of these studies included a control arm and all had smaller sample sizes than the current study. Despite these limitations, they demonstrated the potential benefit of eradication. Of note, these reports included countries and CF centres with much lower MRSA prevalence than the USA, which would be especially relevant in examining rates of MRSA recurrence. A systemic review for the early treatment of MRSA in CF concluded that there were no randomised trials available to assess early eradication.23

The protocol specified antibiotics were based on drug availability, cost, synergy and antibiotic susceptibility in CF MRSA isolates in the USA.16 17 24 Although fusidic acid showed low rates of resistance for US CF MRSA isolates16 and that MRSA eradication protocols outside the USA reported combination therapy with fusidic acid and rifampin, this drug is not approved in the USA. We included nasal or throat decontamination procedures based on the use of mupirocin in non-CF eradication/decontamination25 and the high rate of positive throat cultures in CF.25 Skin decontamination was included based on possible high skin colonisation with SCCmec IV isolates and approaches in non-CF decolonisation.26 Interestingly, despite high rates of SCCmec IV MRSA, skin positivity was rare and the topical skin treatment may not be essential in CF. Further trials comparing our intense protocol to less elaborate treatment approaches are required to demonstrate whether skin decontamination is required.

This study was primarily designed as a controlled trial of MRSA treatment with a short controlled microbiology outcome. Thus, longer-term clinical outcomes after day 28 in our trial are harder to interpret given the very high rate of oral, intravenous and inhaled antibiotics (many with anti-MRSA activity) in both study arms, even in subjects not culturing MRSA.27–29 The participant and treatment heterogeneity after the intervention period limited interpretation of long-term clinical outcomes and we are not able to definitively comment on long-term lower airway eradication. At day 84, a higher proportion of participants in the Rx arm than in the Obs arm were still MRSA-negative. It is difficult to evaluate if recurrence of MRSA is due to persistence not detected by culture or due to reinfec tion and, although repeat isolates were of the same SCCmec type, this method has insufficient sensitivity to address high degree genetic relatedness. Further studies will need to address these questions. Prior literature has demonstrated heavy antibiotics use in US MRSA-positive CF populations.27–29

Two aspects of the study warrant special attention and should be considered in regard to generalisability of results. First, because of poor enrolment rates, the number of study sites was expanded and participants were allowed to be enrolled if they had MRSA isolated from the respiratory tract (sputum or OP culture) at the most recent clinical care visit if this MRSA isolate was available for susceptibility testing. This amendment mirrored common clinical practice and was similar to the approach taken in the Early Pseudomonas Infection Control trial.15 Importantly, when the primary end point was analysed based only on participants who were culture-positive for MRSA at
screening (27/41 in the ITT-E population), the results were similar.

Second, the study was stopped based on an unplanned efficacy interim analysis. Interestingly, early stopping for microbiological efficacy was also initiated in the early inhaled tobramycin eradication trial. At the first planned review, the DMC recommended an unplanned interim efficacy analysis. In response to this unplanned review, additional statistical analyses evaluated the sensitivity of the results to variations in stopping rules (see online supplementary table S1). Because the stopping rule for efficacy was not specified in advance, this sensitivity analysis assessed how sensitive the inference (related to the difference in the proportion of MRSA-negative between study arms) was to a myriad of stopping rules that the DMC could have considered. These estimates of treatment differences adjusted for the corresponding group sequential stopping rule are shown in detail in online supplementary table S1.

This trial was not blinded to either staff or participants because several of the interventions, for example, rifampin could not be blinded. However, the primary end point was an objective measure, that is, culture positivity. This design may have led to higher use of antibiotics in the Obs arm after day 28.

There are a number of important limitations to interpreting the results of this clinical trial. First, only participants ages 4–45 years with early MRSA infection were included. Thus, one cannot infer that this protocol would have a similar treatment effect in patient groups not fulfilling these inclusion criteria. Consistent with the highest incidence of MRSA occurring in mid-childhood in the US CF population, the majority of participants were children with FEV1 >75% predicted (table 1) and the majority could not expectorate sputum. Further, patients presenting in the setting of an acute exacerbation who were culture-positive for MRSA or who had received antibiotics effective against MRSA in the prior 28 days were excluded. These participant characteristics and other exclusion criteria limit the extension of these results to the broader CF population infected with MRSA. Last, the study was not designed to assess the long-term impact of MRSA eradication or effect of repeated treatment MRSA eradication courses. Data gathered in the observational extension portion of the study noted that both Rx and Obs arms received multiple courses of antibiotics with potential MRSA activity.

Our study did demonstrate that spontaneous clearance of MRSA at day 28 does occur at a rate of approximately 13% in those that were culture-positive at screening and 26% in the entire observation arm. Data from the US CF Registry data collected from 1996 to 2006 indicate that among patients ages ≥6 years up to 50% of subjects have only one time positive MRSA cultures or intermittent MRSA infection, however treatment history is missing on these subjects. Such data however do highlight the value of obtaining repeat culturing prior to eradication attempts if one was to employ such a protocol.

**CONCLUSION**

This trial is the first randomised clinical trial to study the microbiological impact of an eradication protocol. While there was a significant difference in microbiological success and evidence towards fewer exacerbations in the Rx arm in this short trial, more questions remain prior to recommending universal early anti-MRSA therapy. These include optimisation of the treatment regimen that is, are all measures necessary and assessing individuals who either have mild exacerbations or are outside the currently selected age range. The high rate of antibiotic use after the primary end point begs the question if a repeat course is indicated in those who remain culture-positive at the end of the treatment. These questions will need further clinical trials and close observation of clinical practice in all countries. However, we did demonstrate that currently available antibiotics with a well established safety profile are effective in early MRSA infection.

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