Eradication of respiratory tract MRSA at a large adult cystic fibrosis centre

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Introduction:
The prevalence of methicillin resistant Staphylococcus aureus (MRSA) infection in the airways of patients with cystic fibrosis (CF) is increasing, and in some populations is now as high as 24% [1]. Large observational studies have demonstrated pulmonary MRSA to be associated with delayed recovery from exacerbations, accelerated decline of FEV₁ in paediatric patients, and higher risk of mortality.
in patients infected for >2 years [1–4]. Current practice in most CF centres is therefore directed towards attempting MRSA eradication. However, as exemplified by a recent Cochrane review, there is at present no general consensus as to the optimum eradication regimen [5,6].

Multiple small uncontrolled studies have suggested various eradication strategies [7–16]. These suggest that dual antibiotic therapy is probably superior over single agent treatment. Several small studies have suggested that combined Rifampicin and Fusidic acid (rif/fus) may be effective, however, regimens varied from several weeks to months of continuous treatment, sometimes in conjunction with nebulised agents such as vancomycin [7–10]. While these regimens suggest that high levels of success can be achieved — with eradication rates at six months of 69–90.9% — problems with tolerability are not infrequently reported [7].

Nearly 600 patients are actively followed at the Royal Brompton Hospital (RBH) Adult CF Centre, with a pulmonary MRSA prevalence of 3.4% (n = 20). Influenced by the available evidence, our strategy towards MRSA eradication has evolved over the past few years, with increasing use of dual antibiotic therapy, in particular oral Rifampicin (300 mg twice daily) with Fusidic acid (500 mg three times daily) from late 2007. Here we report our experience of MRSA eradication since 2007. We have chosen this date to coincide with our change in practice from single to a dual agent strategy. This study is pertinent as there is increasing recognition internationally of the need to develop trials to definitively assess efficacy of MRSA eradication; however, drug choice, treatment duration and drug tolerability are all largely unknown. In the United States, as a result of their relative high prevalence of MRSA infection (~24%), a trial of chronic MRSA eradication is underway (ClinicalTrials.gov NCT01594827). In Europe, a multicentre trial of new MRSA infection was planned but has been suspended before commencement due to trial feasibility and complexities, highlighting the challenging nature of conducting prospective trials in rare conditions across many different countries. The present study was therefore planned to inform practice with the following specific aims: 1) to examine the percentage of sputum isolates negative for MRSA after receiving a specific antibiotic regimen (single or dual agent) with the intention of eradication; 2) to examine the percentage of sputum isolates negative for MRSA after receiving an antibiotic regimen after chronic MRSA infection has been established; 3) to explore factors that predict successful MRSA eradication, including length of treatment and patient characteristics.

Methods

All patients with ≥1 sputum culture positive for MRSA between January 2007 and January 2012 were identified from the hospital microbiology records and local CF sputum database. Patients were defined as either newly or chronically/intermittently infected at point of entry, with “new” infection defined by the presence of ≥3 consecutive preceding negative MRSA cultures over a 12 month period. Electronic patient records were used to record clinical data, antibiotic therapy, treatment duration and sputum microbiology. Baseline clinical characteristics and demographics were taken from the UK CF registry. Data for this is collected for each patient at their annual review and entered on to the registry with informed consent.

Antibiotic treatment recorded for analysis included all oral agents with potential MRSA antimicrobial activity (tetracyclines, chloramphenicol, rifampicin, trimethoprim, fusidic acid, linezolid and co-trimoxazole) given at a time where the most recent sputum cultures available demonstrated ongoing MRSA positivity. Since 2007, our treatment duration policy has been for a minimum of two weeks. The sputum culture is checked prior to stopping therapy and if it remains MRSA positive therapy is continued until sputum is rendered negative (with regular surveillance, up to a maximum of eight weeks). Before 2007, treatment duration was variable but usually 2–4 weeks. As per our hospital guidelines, all MRSA positive patients receive nasal, axillae and perineum swabs, with topical decolonisation. To standardise the analysis and minimise the confounding effect of treatment for exacerbations, intravenous antibiotic courses were excluded from this study. The study focuses on first line treatment for each MRSA/treatment episode as this is most likely to represent a genuine eradication event (and not treatment for an exacerbation); however, subsequent attempts for the same infection episode are also explored.

The primary analysis was the percentage of sputum negative for MRSA after receiving a specific oral MRSA treatment regimen. This was measured after treatment completion (the sample closest to the end of treatment) and is presented as a percent of total infection episodes. If a further course of antibiotics was prescribed for the same infection episode this was also considered treatment failure. After eradication, the persistence of MRSA-negative sputum was measured at six and 12 months. Eradication rates are given overall and subdivided by the different types of treatment regimen (i.e. single or dual agent) for new and chronic MRSA infections. If MRSA persisted (eradication failure) subsequent eradication attempts (i.e. 2nd, 3rd or more) were also examined. As rif/fus was the most commonly prescribed regimen this is presented separately. Baseline clinical parameters (genotype, CF-related diabetes (CFRD), pancreatic status, FEV1, and BMI and co-pathogens in sputum) and length of treatment course were examined to determine their impact on MRSA status. The impact of successful eradication on FEV1, BMI and IV antibiotic requirements was also examined. Data is presented as mean (SD) or median (range) for non-parametric data. Students t-test was used for continuous data, and the Chi square or Fishers exact test was used for categorical data.

Results

Patient characteristics and infection episodes

Fifty patients were initially identified as having one or more positive sputum cultures for MRSA between January 2007 and January 2012. Thirteen were excluded from analysis: four patients transferred to other clinics or underwent transplant ≤12 months post culture results/treatment, and nine had evidence of sporadic positive cultures with no
record of receiving antibiotic therapy that met our inclusion criteria.

Thirty-seven patients were eligible for inclusion (45.9% male, median (range) age 30 (14–62) yrs, median FEV1 58.7 (27.6–111.5) % predicted). 67.6% (n = 25) of these had a newly acquired infection at point of entry (Table 1). The remaining twelve had intermittent or persistent MRSA infection, with a median (range) of 23 (9–27) months infection prior to entry into the study. There were no significant differences between the groups in baseline demographics or clinical parameters. Three of the chronically infected patients were successfully eradicated for >12 months during the study period, but went on to have a subsequent "newly acquired" infection as per our definition, and are therefore included in both groups. Of the 25 patients with a newly acquired infection, 18 had a single episode of infection, six had two new infection episodes (separated by >12 months), and one patient had three.

Eradication attempts

Newly acquired infection

There were 29 first-line treatment attempts for newly acquired infections (single agent, n = 14; dual, n = 15; Table 2 and Fig. 1). Single agents were tetracyclines (64.3%), co-trimoxazole (14.3%), trimethoprim (14.3%) and linezolid (7.1%). Dual agents used included rif/fus for 60% of attempts, and co-trimoxazole and a tetracycline (13.3%). Other combinations were chloramphenicol and septrin, rifampicin and trimethoprim, fusidic acid and minocycline, and chloramphenicol and oxytetracycline, but none of these on more than one occasion. The remaining seven newly acquired infections represented spontaneous clearance after isolated positive sputum cultures — this is accounted for by a period during which our local protocol recommended reconfirmation of MRSA infection with a 2nd sputum culture prior to starting eradication treatment.

Dual regimens were more effective at achieving MRSA eradication post treatment than single agents (84.6% vs 50%), and achieved higher rates of sustained MRSA clearance at six months (57.1% vs 30.8%) and 12 months (46.7% vs 21.4%) but none of the values reached statistical significance. Rif/fus was associated with a higher proportion of sputum negativity than all other dual regimens combined but this did not reach statistical significance: 100% vs 60% post treatment (p = 0.13), 77.8% vs 20% at six months (p = 0.09) and 55.6% vs 33.3% at 12 months (p = 0.6).

The median (range) duration of treatment with dual therapy was 14 (10–42) days (one patient did not complete the two week course due to intolerance) and single therapy was 14 (14–28) days. The duration of rif/fus treatment given in newly acquired infections was 14 (10–42) days. For all first treatment attempts with dual therapy, the eradication rate for shorter (<14 days) courses was 75% (n = 6) and longer courses (>14 days) was 100% (n = 5; p = NS).

Chronic MRSA infection

12 patients were chronically or intermittently infected at point of entry. 11 of these received antibiotic therapy (Table 2), the 12th patient having sporadic positive sputum cultures over a period of three years, without any specific antibiotic being given before spontaneous clearance. Of the 11 who were treated, nine received single agents in the first instance — none resulted in eradication. Both attempts with dual regimens (rif/fus and rif/oxytetracycline) were successful.

New vs chronic MRSA

Comparing eradication rates between new and chronic infections (Table 2), newly infected patients were more likely to be successfully cleared of MRSA after their first attempt at eradication (68%) than those with pre-existing chronic infection (18.2%, p = 0.01). Single agents were more likely to achieve eradication in new infections (6/12; 50%) compared to chronic (0/9; 0%; p = 0.01). In both groups of patients, dual antibiotic regimens demonstrated equivalent rates of MRSA eradication post treatment completion (84.6% (11/13) vs 100% (2/2); p = NS) but the numbers were very small.

Subsequent eradication attempts

Subsequent eradication attempts for the same infection episode were common (Table 2). Overall 131 courses were prescribed (new MRSA = 61: 1st attempt, n = 29; 2nd attempt, n = 14 and ≥3 attempts, n = 18; chronic MRSA = 70: 1st attempt, n = 11; 2nd attempt, n = 9 and ≥3 attempts, n = 50). In patients with newly acquired infection, treatment given as a 1st attempt at eradication achieved higher success rates than subsequent 2nd and ≥3rd attempts (comparing 1st attempt outcomes with ≥3rd attempt directly, single therapy eradicated 50% vs 11%, p = 0.16; dual therapy eradicated 84.6% vs 25%, p = 0.02).

In those with chronic infection, there was some evidence of effectiveness with subsequent eradication attempts: rif/

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Table 1 Baseline population demographics.

<table>
<thead>
<tr>
<th></th>
<th>All patients with MRSA (n = 37)</th>
<th>Newly infected (n = 28)</th>
<th>Chronic/intermittent infection (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male (n)</td>
<td>45.9 (17)</td>
<td>50 (14)</td>
<td>41.7 (5)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>30 (17–62)</td>
<td>30 (17–62)</td>
<td>26 (22–48)</td>
</tr>
<tr>
<td>% Homozygous ΔF508 (n)</td>
<td>45.9 (17)</td>
<td>50 (14)</td>
<td>41.7 (5)</td>
</tr>
<tr>
<td>% Pancreatic insufficient (n)</td>
<td>86.5 (32)</td>
<td>89.3 (25)</td>
<td>83.3 (10)</td>
</tr>
<tr>
<td>% CFRD (n)</td>
<td>29.7 (11)</td>
<td>28.6 (8)</td>
<td>33.3 (4)</td>
</tr>
<tr>
<td>Median BMI (range)</td>
<td>21.9 (16.6–29.8)</td>
<td>22.0 (16.6–29.8)</td>
<td>21.5 (16.6–26.8)</td>
</tr>
<tr>
<td>Median FEV1 (range)</td>
<td>59.0 (27.6–111.5)</td>
<td>61.9 (28.2–107)</td>
<td>54.3 (27.6–111.5)</td>
</tr>
</tbody>
</table>

* 25 newly infected at point of entry + 3 newly infected >12 months post clearance of chronic infection.
fus was used at the 3rd attempt and resulted in sputum negativity in 80% (4/5) of treatment episodes (it was not used in 2nd attempt). Post single agent therapy, eradication rates of 0% (0/9) in 1st and 2nd attempts, and 13.5% (5/37) in 3rd attempts were seen.

Rifampicin and fusidic acid
In total this regimen was used on 27 occasions (Fig. 1), in 20 different patients (9 courses were given as a first attempt at eradication). For all courses given in both newly and chronically infected patients and at any stage of infection, rif/fus led to successful eradication in 82.6% (19/23) post treatment, and at 6 and 12 months, persistent sputum negativity was maintained in 68% (17/25) and 58.3% (14/24), respectively. Two courses were discontinued: one patient did not tolerate the treatment (due to nausea), and one other course was not completed due to deranged liver function tests. Two further patients only had results at 6 months post treatment (both were negative) and one had no result at 12 months though had no further antibiotics prescribed. The duration of treatment with rif/fus varied between 10 and 56 days, but longer courses of treatment were not found to be more effective, with a median (range) of 14 (10–56) days for successful eradication and 28 (14–42) days for unsuccessful clearance at 3 months (p = NS).

**Clinical characteristics and their relationship to MRSA status**

Clinical parameters were compared for both newly and chronically infected patients to determine factors associated with successful eradication after first-line treatment (Table 3). In newly infected patients, there was a trend towards a higher prevalence of ΔF508 homozygosity (62.5% vs 41.2%), CF-related diabetes (50% vs 23.5%), and pancreatic insufficiency (100% vs 86.7%) in those who failed to eradicate MRSA, but this did not reach statistical significance. Successful eradication was associated with higher pre-treatment FEV1% predicted but again this did not reach statistical significance: 62.3% vs 49.7% (p = 0.11). Similar trends were seen in chronically infected patients: 55.6% homozygous ΔF508 (vs 0% in eradicated patients), 22.2% CFRD (vs 0%), 88.9% pancreatic insufficient (vs 50%), and FEV1% predicted was similarly lower at baseline (49.1% vs 85.1%) in patients in whom eradication failed, though these trends were not statistically significant.

Clinical parameters (FEV1, BMI and IV antibiotic days) were taken from two sequential annual review encounters, either side of the MRSA treatment episode, to determine their relationship to MRSA status. No significant difference in any parameter was detected between the eradication success or failure groups.
For the 28 patients with newly acquired infection, at the time of initial MRSA positivity, 21 (72.4%) had evidence of concurrent Pseudomonas aeruginosa, and Aspergillus fumigatus was present in 17.2% (n = 5). One patient had concurrent Achromobacter xylosoxidans, but none had evidence of non-tuberculous mycobacteria or Burkholderia cepacia at the time of first positive MRSA culture. Presence of P. aeruginosa or A. fumigatus did not affect the likelihood of successful MRSA eradication. Of those with peripheral swab results available, 38.9% (7/18) had one or more topical swab positive for MRSA, though this too had no bearing on subsequent respiratory tract MRSA clearance.

Discussion and conclusions

The present study is timely and relevant as the clinical importance of MRSA infection of the CF airways is being increasingly recognised but with limited data to guide practice. Our study suggests both that dual oral antibiotic treatment, particularly rif/fus, may be more effective than single agent antibiotic use and, importantly, that protracted courses may not be necessary.

The prevalence of MRSA has been steadily increasing in most countries over the past decade, ranging from 2.6% in the UK to 24% in the USA [1,17]. The reasons for this increasing prevalence are unclear although the widespread use of broad spectrum antibiotics is speculated to be a factor. Although the pathogenic potential of MRSA is not fully understood, it is now widely accepted to be associated with worse clinical outcomes [1,2,4] with a large USA registry-based study demonstrating an association with mortality [3]. However, there is limited data on the most effective strategy for treating MRSA and there is no consensus as to the timing, type and duration of treatment. Uncontrolled studies suggest that MRSA can be eradicated [5,7,8,10] and extrapolating data from other eradication trials (e.g. for P. aeruginosa) suggests that MRSA eradication may need to be attempted early.

Dual therapy with rif/fus has previously been evaluated in small cohorts. Garske et al. [7] demonstrated efficacy in a small number of chronically infected patients (71% eradication; n = 5) with a prolonged eradication regimen of six months, although confounding from additional antistaphylococcal antibiotics over the study period may have occurred. Vanderhelst et al. [8] demonstrated similarly high levels of success in their prospective observational study, eradicating MRSA in 10/11 (91%) of chronically infected patients by a similar treatment regimen to that of Garske et al. Both of these studies found rif/fus to be broadly well tolerated, although the incidence of gastrointestinal side effects was not insignificant (2/7 and 5/11, respectively). A retrospective study by Doe et al. reported successful eradication in 81% of their cohort overall, including 61%
success with the combination of nebulised vancomycin (administered for the first five days as an inpatient) and two oral antibiotics [10]. Oral antibiotics (most commonly rif / fus) were used for a minimum of six weeks.

With our current protocol of combined rif / fus, eradication rates of 100% immediately post treatment and 77.8% at six months were obtained for new MRSA infections. These are comparable to previous studies and were achieved without either the requirement for concurrent nebulised vancomycin or the need for several weeks or months of therapy. Furthermore, albeit in a small number of patients, rif / fus also demonstrated efficacy in eradicating chronic MRSA, even following multiple prior attempts at eradication with alternative agents. Generally using shorter regimens than have been employed elsewhere, we report high rates of tolerability with only 2/27 (7.4%) courses discontinued due to gastrointestinal symptoms or adverse effects. Shorter courses, particularly of multiple antibiotics, are more attractive to the patient and clinician as they are convenient, easier to monitor and less likely to lead to early discontinuation due to intolerance and poor compliance.

In comparison to other studies, our study population is amongst the largest and benefits from 12 months follow-up for all patients, providing important clinical information on eradication of both chronic and newly acquired MRSA, rates of subsequent re-infection and the likelihood of successful eradication with further courses of treatment. The majority of the cohort received dual antibiotics, of which rif / fus was the most frequent. Whether or not newer antibiotics, such as the oxazolidinone, linezolid, would be more effective is yet to be elucidated; early studies suggest it may have a role [18] although it could be limited by its adverse event profile (optic neuropathy and myelosuppression) and cost. Shorter courses, particularly of multiple antibiotics, are more attractive to the patient and clinician as they are convenient, easier to monitor and less likely to lead to early discontinuation due to intolerance and poor compliance.

We recognise the limitations of our study, including its retrospective design. We aimed to assess antibiotic therapy for targeted eradication only, but accept some treatment may have been given for pulmonary exacerbations. Some patients may have also received additional antibiotic therapy (e.g. from their general practitioner), but the impact of this is likely to have been small as our patients are reviewed on average every 2–3 months and encouraged to liaise with the CF centre directly if there is any change in clinical status. Despite all relevant patients being included over a 5-year period from a large adult CF centre, our study population remains small, limiting statistical power and interpretation of comparisons between groups. Inclusion of all antibiotics given at all stages of infection also limits the power of the study and the potential to identify statistically significant trends but we have included this as, in our opinion, it provides ‘real world’ evidence of eradication practice with informative results — e.g. eradication success for the same infection episode even when attempted previously.

Additional considerations for future studies should include the impact of MRSA virulence factors as these may affect rates of eradication success. MRSA strains are distinguished by the Staphylococcal Cassette Chromosome (SCC) mec type of which at least eight subtypes exist, each with varying levels of antibiotic resistance. Additional virulence factors, such as the leucocytolytic toxin Panton-Valentine leucocidin, are harboured by S. aureus and are more frequently expressed in MRSA than methicillin-sensitive strains. Small colony variant strains may also develop as a result of antibiotic exposure and are associated with persistent infection and more advanced lung disease.

From our study we conclude that MRSA eradication is achievable and that, generally, our current treatment regimens are well tolerated. Dual antibiotic therapy appears to be more effective than single agent regimens in eradicating MRSA from the sputum of adult patients; in particular, combination rif / fus acid appears to be well tolerated and effective in both new and chronic MRSA infections. Moreover, our findings suggest that a relatively short treatment duration may be adequate, and that eradication may still be achievable even after prolonged periods of infection, though may be harder to achieve in patients with lower FEV₁, or other features such as pancreatic insufficiency, CFRD or ΔF508 homozygosity. These findings now require validation through large, well powered, prospective studies, with the aim of definitively determining the optimal eradication strategy and the effect MRSA clearance has on clinical outcomes.

Conflict of interest

There are no conflicts of interest.

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References

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