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

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Summary
Introduction: The prevalence of MRSA in patients with CF is increasing. There is no consensus as to the optimum treatment.
Method: An observational cohort study of all patients with MRSA positive sputum, 2007–2012. All eradication attempts with subsequent culture results were reviewed. Single vs dual antibiotic regimens were compared for both new and chronic infections.
Results: 37 patients (median FEV_1 58.7 (27.6–111.5)% predicted) were identified, of which 67.6% ($n = 25$) had newly acquired MRSA. Compared with single regimens, a high proportion of dual regimens achieved MRSA eradication (84.6% vs 50%; $p = 0.1$) for new infections. Rifampicin/Fusidic acid was associated with high success rates (100% vs 60% for other dual regimens ($p = 0.13$)). Compared with new infections, chronic MRSA was much less likely to be eradicated (18.2%, $p = 0.01$).
Conclusion: Combined antibiotic therapy, particularly Rifampicin/Fusidic acid, is a well-tolerated and effective means of eradicating MRSA in patients with cystic fibrosis.

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 FEV_1 in paediatric patients, and higher risk of mortality

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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, FEV_1, and BMI and copathogens in sputum) and length of treatment course were examined to determine their impact on MRSA status. The impact of successful eradication on FEV_1, 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