Treatment decisions for MRSA in patients with cystic fibrosis (CF): when is enough, enough?

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Treatment of infection in cystic fibrosis (CF) lung disease should be based on identifying which organisms warrant treatment, requiring evidence that the pathogen leads to worse outcomes and that intervention yields better clinical outcomes. This has been demonstrated for *Pseudomonas aeruginosa*, where eradication of early infection and suppression of chronic infection have become the standard of care. This approach has not been broadly adopted for *Staphylococcus aureus*, in part because of insufficient evidence demonstrating an association with worse outcomes and treatment has not proven better outcomes. However, there is a rising concern about methicillin-resistant *S. aureus* (MRSA). MRSA infection in patients with CF has been associated with more severe pulmonary disease and poorer clinical outcomes.^{1–3}

Rates of MRSA infection have increased dramatically and now exceed 25% of the CF population in the USA, paralleling rates in the general community.⁴ Notably, prevalence rates of MRSA are significantly lower in other countries including the UK and Australia (each 2.6%).^{5–6} Given these observations, efforts to treat MRSA would seem relevant, but evidence of treatment benefit is lacking. Until now, treatment approaches for MRSA have been anecdotal and decision-making has been supported by small studies.^{7–15}

The results of a prospective, open-label randomised study of the treatment of early MRSA infection in patients with CF are reported.¹⁶ The primary endpoint was a microbiological one—could they render the patient culture negative, often assumed to represent eradication? Participants were randomly allocated to treatment or a period of observation. Treatment included antibiotics for 14 days

in addition to hygienic measures aimed to reduce nasal, cutaneous and domestic environmental colonisation. The key findings of the study were a higher proportion of patients without MRSA in airway cultures at 28 days (82%—treatment arm vs 26%—observation arm).

Two important trial conduct issues were identified during the study. First, there was a change in the inclusion criteria for study entry and second an unplanned interim analysis resulting in a premature termination of the trial. Modification of the microbiology inclusion criteria allowed a broader definition of early MRSA infection (from culture positive at screening to 'recent' culture). The purpose for the change was poorer than anticipated recruitment to the study in part because of negative cultures at screening, although there are competing clinical trial programmes (particularly CFTR modulators) that may adversely impact the study recruitment for antibiotic trials.¹⁷ There are other potential reasons for poor recruitment. Patients may elect to skip antibiotics because they feel well and there is a lack of evidence of persistence of MRSA, while others (and possibly clinicians) elect not to wait the observation period before commencing antibiotics,¹⁸ an example of practice evolving in the absence of evidence. In this study, the investigators elected to use a short observation period as the control arm of the study. Although this might alarm some clinicians and families, this is an appropriate aspect of the trial. Treatment in this setting is not a standard of care, as it is for *Pseudomonas*; also initial detection of MRSA does not always lead to chronic infection. Finally, the study allowed treatment at the completion of this short duration trial.

The authors suggest that treatment based upon a historical culture would be consistent with clinical practice, which is likely correct, but still problematic for a clinical trial as it resulted in some group imbalance. Specifically, a larger proportion of subjects allocated to the treatment group were culture negative at screening (50% vs 28%). When evaluating only those subjects who were culture positive

at screening, there was still a treatment difference between the groups. Rigorous sensitivity analyses to address potential bias also suggest the impact of this protocol change did not materially change the outcome of the primary study outcome.

How shall we consider the implications of a positive culture of MRSA and when does it mean chronic infection? While not well defined in the literature transient infection with MRSA is well known and could be as high as 50% in some studies^{19–20} and the authors state 30% of patients with a positive culture reported in the US Cystic Fibrosis Foundation (CFF) Patient Registry do not have chronic infection. Several other studies suggest chronic infection is not universal but is difficult to estimate due to early treatment.^{10–14–15} As noted in this trial, patients may be intermittently culture positive, both in demonstrating negative cultures at screening (40% overall) and another 13% of subjects who were culture positive in the observation arm were culture negative at Day 28. Defining infection as early, intermittent or chronic may be more difficult than it has been for *P. aeruginosa*.

A challenge of studying airway infection in children^{21–22} and even a growing number of adults with CF²³ is choosing the endpoint sampling strategy. This study used oropharyngeal swabs as the source for cultures to assure consistency, which is arguably best for a clinical trial. However, oropharyngeal samples can incorrectly assign microbiological status.^{24–25} In the future, sputum induction may be a more appropriate source of sampling for microbiological endpoints.^{23–26}

The second trial conduct issue in this study was an unplanned interim analysis and its implications. The planned study population was 90 participants, and importantly, the data safety monitoring committee (DSMC) prematurely stopped the trial (~50% recruitment) due to a significantly higher rate of MRSA clearance in those receiving active therapy. No safety issues were raised during the analysis. It is unfortunate the study was not allowed to complete enrolment; the stopping rules were applied using the entire population but would not likely have been met if using only those who were culture positive at screening.

Interestingly, in this study, several patients (n=6) in the observation arm received MRSA-active antibiotics (including rifampicin and sulfamethoxazole/trimethoprim) highlighting the complexity of how to handle concomitant medications even in a short-term trial as described in this study.

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What questions remain after this randomised controlled trial (RCT)?

1. What is the optimal trial design? For *Pseudomonas* eradication trials, typically culture results shortly after completion of treatment are used, but monitoring for a prolonged duration to see when the cultures returned positive, suggesting new infection. Recurrence rates of MRSA in both arms of the study were significant by day 168 (and 84) and may suggest ongoing infection (or reinfection) despite the negative cultures at the trial completion. Would a study such as Early *Pseudomonas* Infection Control (EPIC)²⁷ in which subsequent treatment with MRSA therapy be based on a routine schedule or culture result be of greater relevance?
2. When should MRSA eradication be initiated? If following the approach to 'early' *Pseudomonas* infection, then on first culture would be desired; however, this is likely to lead to 'over-prescribing' in at least one in three patients.^{9 20} Immediate treatment for patients and clinicians may be desirable when therapies are able to be 'pulled off the shelf'.
3. What is the optimal therapy? Whether two drugs are required in all cases remains uncertain and the impact of cutaneous and mucosal colonisation is unclear yet adds to the 'burden of therapy'. The adherence to both antibiotic and hygiene regimens was disappointing for such a short duration study. The authors appropriately question the need for the hygiene regimen, which may allow for a simpler study design. In a recent study, eradication failure was associated with cutaneous colonisation, suggesting decolonisation may also be important.¹⁴ An alternate approach highlighted by a short-term phase-II trial of inhaled vancomycin has demonstrated some promise, although a longer-term trial is required to demonstrate efficacy and safety.²⁸
4. How generalisable are these results? Interestingly, the vast majority of patients were young and had mild lung disease. In the USA, incidence rates have been higher in younger patients.²⁹ This is not a finding in all countries where prevalence of MRSA increases with increasing age. In the setting of significant lung disease, the effectiveness of eradication may be lower (especially when MRSA is multi-resistant). Rates of long-term eradication from sputum appear not to

exceed 50% and could be much lower.^{9 10} MRSA susceptibility varies globally^{19 20 30} and may include *S. aureus* which is multiresistant and where sodium fusidate (not licenced in the USA) and rifampicin are prescribed.^{9 10 14 15}

In conclusion, this study has addressed an important question facing the CF community. Although there are some challenges in the analysis, they have demonstrated that antibiotic treatment of early MRSA may result in a reduction in positive cultures. They have also revealed several questions that will be relevant for the design of the next study, which must be done if we are to ever know how best to manage patients who have MRSA infection. It is notable that although the authors provided clinical data on the patients it is premature to gauge any conclusions as to whether there is a clinical benefit from this therapy. The purpose of this study was to see whether there could be a microbiological effect. Let us hope that standard treatment practices will not evolve such that additional studies cannot be done. The authors are to be congratulated for undertaking the first RCT for MRSA infection in CF.

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