Antibiotics for prevention of respiratory exacerbations

MRSA eradication in CF

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Background

Staphylococcus aureus (SA) is among the earliest bacterial pathogens detected in infants and children with cystic fibrosis (CF) and is the most prevalent organism in the pediatric CF population, with peak prevalence observed between 11 and 15 years of age. The emergence of methicillin-resistant *S. aureus* (MRSA) over the past decade has drawn considerable attention to this pathogen. In particular, there has been a rapid increase in MRSA prevalence among people with CF, exceeding 25% across CF centers in the United States. Epidemiological studies suggest that chronic, but not intermittent, MRSA infection is associated with worse clinical outcomes. Given the challenges inherent in treating chronic lung infections in CF, the optimal approach to the onset of MRSA infection remains unclear.

The role of MRSA in CF has been extensively reviewed by Goss et al (Goss CH, 2011), by Parkins et al (Parkins MD, 2015), by Muhleback (Muhlebach MS, 2017) and by Akil (Akil N, 2018). Experience from selected CF centers is also available (Hall H, 2015), (Kiefer A, 2018). Furthermore, analyses from the Cystic Fibrosis Foundation (CFF) Patient Registry demonstrated that between 2006 and 2012 the annual prevalence and incidence of MRSA increased across all age groups (Salsgiver EL, 2016) and that receiving care at a CF center with higher MRSA prevalence is associated with an increased risk of MRSA acquisition (Jennings MT, 2017). More recently, a US registry-based study reported that Hispanic people with CF younger than 25 years have an increased risk of acquiring methicillin-susceptible *S. aureus* (MSSA) and acquire both MSSA and MRSA at an earlier age. These differences in *S. aureus* acquisition may contribute to increased morbidity among Hispanic people with CF (McGarry ME, 2023).

Issues

- Should initial or new bacterial infection with MRSA be treated?
- If eradication of MRSA is attempted, what protocol should be used?
- Is it possible the eradicaton of persistent MRSA infection in CF?

What is known

One CDSR is available (Lo DK, 2022), whose conclusions are that early eradication of MRSA is possible in people with cystic fibrosis, with one trial demonstrating superiority of active MRSA treatment compared with observation only in terms of the proportion of MRSA?negative respiratory cultures at day 28. However, by six months, the proportion of participants who remained MRSA?negative did not differ between treatment arms in either trial. Moreover, the longer?term clinical consequences in terms of lung function, mortality and cost of care, remain unclear. Based on the available evidence, it is the opinion of the authors that whilst early eradication of respiratory MRSA in people with cystic fibrosis is possible, there is not currently enough evidence regarding the clinical outcomes of eradication to support the use of the interventions studied.

There are no current recommendations or guidelines specific for MRSA in CF. A prophylactic MRSA protocol would be very concerning and likely enhance emergence of further resistance.

A non-blinded trial from US showed that an eradication protocol for newly acquired MRSA (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) had microbiological efficacy with a large treatment effect (Muhleback MS, 2016).

A retrospective analysis evaluated the results obtained, in a single center experience, combining oral rifampicin and fusidic acid, inhaled vancomycin, nasal mupirocin, local antiseptic treatment and hygienic directives, all of which were applied for only 7 days during an inpatient hospital stay (Kiefer A, 2018). 86% successful eradication of MRSA (6/7 subjects) was achieved upon first treatment using the protocol described above.

Recently, a blinded RCT from US evaluated a protocol of eradication in subjects with CF and documented persistent MRSA infection (Dezube R, 2019). All participants received oral antibiotics, topical decontamination, and environmental cleaning and were randomized to receive inhaled vancomycin or inhaled placebo. The primary outcome was the difference in MRSA eradication rates one month after completion of the treatment protocol.There was no difference in the primary outcome: 2/10 (20%) of subjects in the intervention group and 3/15 (20%) in the placebo group had a MRSA negative sputum culture one month after treatment. There were no statistically significant differences in the rates of MRSA eradication at the end of treatment or three months after treatment completion.

In a randomized multicenter trial conducted on patients with new-onset MRSA infection Italian researchers evaluated the efficacy of an early eradication treatment (arm A) compared with an observational group (B). Arm A received oral rifampicin and trimethoprim/sulfamethoxazole (21 days). The main result was that a 24.7% higher clearance of MRSA was observed in the active arm than in the observational arm at 6 months. Patients in the active arm also had favorable FEV1 and BMI tendencies. (Dolce D, 2019)

A single?center, retrospective study of children age 30 days to 17 years evaluated an eradication regimen of dual oral antibiotic therapy (rifampin and either TMP?SMX or minocycline was given twice daily for 14 days), topical decontamination, and environmental decontamination (Belarski E, 2020). The authors conclude that an extensive eradication protocol may lead to an increased clearance rate of long?term CF respiratory cultures but does not appear to affect clinical outcomes.

Unresolved questions

To date, no conclusive studies have demonstrated whether early aggressive treatment of initial MRSA respiratory infection can prevent chronic colonization or improve long-term clinical outcomes. Moreover, eradication of established MRSA infection remains particularly challenging.

A recent trial enrolled people with CF and incident MRSA infection into the *Staphylococcus aureus* Resistance–Treat Early and Repeat (STAR-ter) protocol, in which participants received a combination of oral antibiotics and topical decolonization of the nares and throat. This open-label, multicenter interventional trial is currently ongoing in the United States and includes individuals with CF who have a new MRSA isolate identified from the respiratory tract (oropharyngeal swab, sputum, or bronchoscopy) at a clinical encounter.

Aim of the study is to evaluate the microbiologic efficacy and safety of a streamlined treatment for early onset methicillin-resistant staphylococcus aureus (MRSA) in patients with cystic fibrosis. The Estimated Completion Date is December 30, 2025. (https://www.ce

Further studies are needed to determine whether early eradication protocols effectively eliminate MRSA and whether eradication translates into improved clinical and microbiological outcomes in CF. It is also essential to assess whether such treatments increase the risk of acquiring other resistant organisms or cause additional drug-related adverse effects.

Data on the early clinical impact of new MRSA isolation are required. While several authors suggest that eradication may be reasonable to attempt, more evidence is needed before it can be routinely recommended for all patients.

Keywords

Bacterial Infections; Burkholderia cepacia; Colonization; Infection; Pneumonia; Respiratory Tract Infections; Staphylococcus aureus; Aminoglycosides; Anti-Bacterial Agents; Carbapenems; Cephalosporins; Monobactams; Others anti-bacterial agents; Penicillins; Quinolones; Tetracyclines;