Antibiotics for prevention of respiratory exacerbations

Prophylactic use of oral antistaphylococcal antibiotic

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Background

Staphylococcus aureus (SA) has long been detected in the airways of patients with cystic fibrosis (CF) and has been considered a potential precursor to subsequent infection with *Pseudomonas aeruginosa* (PA); it is also associated with increased lower airway inflammation. SA typically causes pulmonary infection early in life, particularly in young children with CF. Recently, a US registry-based study reported that Hispanic people with CF (pwCF) younger than 25 years have an increased risk of acquiring methicillin-susceptible *S. aureus* (MSSA) and acquire both MSSA and methicillin-resistant *S. aureus* (MRSA) at an earlier age. These differences in *S. aureus* acquisition may contribute to increased morbidity among Hispanic pwCF (McGarry ME, 2023).

Accordingly, some authors have advocated for prophylactic therapy against SA, a strategy recommended in the UK and several other countries (UK Cystic Fibrosis Trust Antibiotic Working Group guidelines) but not adopted by clinical practice guidelines in the United States (Cystic Fibrosis Pulmonary Guidelines).

The aim of prophylactic antibiotic use in this population is to reduce infection and inflammation in the developing lung and to delay the onset of bronchiectasis. However, antibiotics may have adverse effects, and long-term use could promote infection with other pathogens, including PA.

An alternative perspective focuses on the treatment of chronic SA pulmonary infection and its effects on lung function, sputum clearance of *S. aureus*, incidence of adverse events, quality of life, frequency of acute pulmonary exacerbations, nutritional outcomes, and the new isolation of bacterial pathogens, including PA.

A review describes ongoing research addressing the long-standing and controversial issues surrounding antibiotic prophylaxis (Hurley MN, 2018)

Issues

To assess if continuous oral antibiotic prophylaxis to prevent the acquisition of SA versus no prophylaxis in people with CF:

1. improves clinical status, lung function and survival;
2. causes adverse effects (eg gastrointestinal, cutaneous, opportunistic fungal infections);
3. leads to fewer isolates of common pathogens from respiratory secretions;
4. leads to the emergence of antibiotic resistance and colonisation of the respiratory tract with PA.

Other issues regard the chronic use of azithromycin in CF patients and its effect on SA and the role of treatment for chronic SA pulmonary infection.

What is known

One CDSR studied this argument (Rosenfeld M, 2020). It included four studies of anti-staphylococcal antibiotic prophylaxis in children with CF, with data from 401 participants. The authors tested the following hypotheses to investigate whether prophylaxis:
1. improves clinical status, lung function and survival;
2. leads to fewer isolates of *Staphylococcus aureus*;
3. causes adverse effects (e.g. diarrhoea, skin rash, candidiasis);
4. leads to fewer isolates of other common pathogens from respiratory secretions;
5. leads to the emergence of antibiotic resistance and colonisation of the respiratory tract with *Pseudomonas aeruginosa*.

Anti-staphylococcal antibiotic prophylaxis may lead to fewer children having isolates of Staphylococcus aureus, when commenced early in infancy and continued up to six years of age. The clinical importance of this finding is uncertain. Further research may establish whether the trend towards more children with CF with Pseudomonas aeruginosa, after four to six years of prophylaxis, is a chance finding and whether choice of antibiotic or duration of treatment might influence this.

There is insufficient evidence to say whether the use of anti-staphylococcal antibiotic prophylaxis in older children or adults is beneficial or harmful. For this reason, caution should be exercised, if prophylactic anti-staphylococcal antibiotics are used in older individuals or for longer periods.

Treatment with azithromycin was associated with a reduced risk of SA acquisition but was not associated with increased eradication. No effect was evident on respiratory function. There are some concerns reporting an increased risk of acquiring macrolide-resistant SA for those patients on azithromycin whereas there is neither evidence of increased risk of acquiring methicillin-resistant SA (MRSA) at either 6 or 12 months following treatment with azithromycin compared to placebo nor of increased risk of acquiring small-colony-variant SA.

One CDSR (Ahmed MI, 2018) focused on the evidence regarding the effectiveness of long-term antibiotic treatment regimens for chronic infection with methicillin-sensitive SA (MSSA) infection in subjects with CF to determine whether this leads to improved clinical

and microbiological outcomes. No randomised controlled trials were identified which met the inclusion criteria for this review and there is no agreement on how best to treat long-term infection.

A longitudinal observational study (Hurley MN, 2018) examined children recruited from birth (or their first registry entry in the period) and followed until the age of 4 years (1500 days) using UK CF Trust and US CF Foundation Registries, 2000-2009, in order to evaluate the impact of anti-staphylococcal antibiotic prophylaxis (recommended in the UK, but recommended against in the US). Time to first SA and PA detection in the UK/US cohorts were compared using a Cox proportional hazards model. The risk of first detection was greater in US compared to UK for SA (hazard ratio (HR) 5.79; 95% CI: 4.85, 6.90; p<0.001) and PA (HR 1.92; 95% CI: 1.65, 2.24; p<0.001). The UK analysis compared 278 children receiving flucloxacillin and 306 receiving no prophylaxis. Flucloxacillin was not associated with a reduced risk of SA (HR 1.22; 95% CI: 0.74, 2.0; p=0.43), but was associated with an increased risk of PA (HR 2.53; 95% CI: 1.71, 3.74; p<0.001) detection. Data from this study are quite difficult to be interpreted. UK and US registries collect data in different ways (annual data vs encounter data); cultures rely on oropharyngeal and cough swabs, which are known to have relatively low sensitivity and specificity for lower airway infection.

Recently, a retrospective study from Australia showed that adherence to anti-staphylococcal prophylaxis in the first 2 years of life is not associated with a decrease in S. aureus in the lower airways, questioning the value of such prophylaxis. (Holmes M, 2025)

Unresolved questions

Important questions, such as the impact of prophylaxis on antibiotic resistance patterns and patient survival, remain unanswered. The polymicrobial nature of CF lung infection is increasingly recognized. People with CF who have preserved lung function harbor greater microbial diversity in the airways than those with poorer lung function or more frequent exacerbations. The effect of prophylactic antibiotics on this complex ecosystem remains unknown. Chronic exposure to prophylactic antibiotics may disrupt the fecal and/or respiratory microbiome, potentially creating a favorable environment for opportunistic pathogens such as *P. aeruginosa*.

These issues can only be adequately addressed through long-term follow-up studies with careful bacteriological and clinical surveillance. Randomized interventions evaluating antibiotic prophylaxis, coupled with systematic data collection through existing CF registries, may represent a suitable model for future research.

Moreover, there is a clear need for well-designed clinical trials capable of providing robust evidence to inform the optimal management strategy for chronic MSSA infection in people with CF.

An ongoing UK trial [CFSTART - https://www.cfstart.org.uk/) may address several of these unresolved questions. A total of 480 participants have been recruited across 64 sites. Although no results are currently available, the research team anticipates reporting meaningful findings in 2027.

Keywords

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