Antibiotics for prevention of respiratory exacerbations

Prophylactic use of oral antistaphylococcal antibiotic

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Background

Sthaphylococcus aureus (SA) has long been found in the airways of Cystic Fibrosis (CF) patients and has been thought to be a predecessor of later infection by *Pseudomonas aeruginosa* (PA) and appears to be associated with increased lower airway inflammation. SA causes pulmonary infection first of all in young children with CF. As such, some have advocated for prophylactic therapy against *SA* a strategy that is being recommended in the UK and other countries (UK Cystic Fibrosis Trust Antibiotic Working Group guidelines) but has not been adopted by clinical practice guidelines in the US (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 slow the onset of bronchiectasis.

However, antibiotics could have adverse effects and long-term use might lead to infection with other germs, such as PA.

Another possible point of view is the role of treatment for chronic SA pulmonary infection, in relation to lung function, sputum clearance of S. aureus, incidence of any adverse effects, quality of life, incidence of acute pulmonary exacerbations, effects on nutrition and new isolation of bacterial pathogens including PA.

A recent review describe research underway that will address the long-held contentious issues of 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 (Smith AR, 2017). It included four studies of anti-staphylococcal antibiotic prophylaxis in children with CF, with data from 401 participants.

Significantly fewer children with CF will have SA in upper respiratory secretions when anti-staphylococcal antibiotic prophylaxis is prescribed for the first 6 years of life. However, this finding is clinically uncertain, as it has not shown that is associated with an improvement in clinical outcome measures. The currently available evidence does not allow conclusions to be drawn regarding the effect of prophylaxis on acquisition of PA. There was no significant difference in the number of isolates of PA between groups (low quality evidence), though there was a trend towards a lower cumulative isolation rate of PA in the prophylaxis group at two and three years and towards a higher rate from four to six years. There was no significant difference in the rate of common adverse effects.

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.

One CDSR (Rosenfeld M, 2020) assessed if continuous oral antibiotic prophylaxis prevents the acquisition of *Staphylococcus aureus* versus no prophylaxis in people with cystic fibrosis, and 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*.

The authors conclude that 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. However, the clinical importance of this finding is uncertain. There is a need of further research to 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.

Unresolved questions

Important questions, such as the influence of prophylaxis on antibiotic resistance patterns and on patient survival, will remain unanswered. The polymicrobial nature of CF lung infection is increasingly appreciated. Subjects with CF with good lung function host greater lung microbial diversity compared to their counterparts with poorer lung function or who experience frequent exacerbations. The effect of prophylactic antibiotics upon this complex ecosystem is unknown. It may be that chronic exposure to prophylactic antibiotics disrupts the fecal and/or respiratory microbiome, providing a favourable ecosystem for opportunistic bacteria like *P. aeruginosa*.

These issues can only be addressed by long-term follow-up studies, with careful bacteriological and clinical surveillance. It may be that a randomised intervention with antibiotic prophylaxis coupled with data collection via the existing CF registries might provide a suitable model for future research.

Moreover it should be highlighted the need to organise well-designed trials that can provide evidence to support the best management strategy for chronic MSSA infection in subjects with CF. An ongoing trial from UK [CFSTART - (http://www.ne

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;