Antibiotics for prevention of respiratory exacerbations

Scheduled antibiotics every 3-4 months / symptom-based treatment

Code: 105 **Updated:** December 01, 2024

Background

The treatment of chronic infection in cystic fibrosis (CF) has the aim to maintain good lung function, to improve quality of life and to reduce mortality. There is no international consensus on the management of chronic infection in people with CF.

Two main strategies are widely practised. The elective regimen is to administer regular courses of intravenous (IV) antibiotics usually every three-months, regardless of the clinical status.

The alternative regimen is prompt treatment of acute exacerbations as determined by clinical or radiological findings or deterioration in lung function parameters (symptomatic regimen).

An alternative strategy could be the use of the oral route of administration of antibiotics.

The main attention about treatment of chronic infection is versus Pseudomonas aeruginosa (PA). Further microorganisms are relevant in the evaluation of chronic lung disease in CF (such as B. Cepacia, S. Maltophilia, MSSA and MRSA). Recent updates on the role of antimicrobial therapy in CF are available (Waters V. et al 2015)(Epps QJ, 2020)(Magréault S, 2021)(Green HD).

An interesting point, strictly related to the intensive use of antibiotics in CF patients is the role of antibiotic adjuvant therapies, agents that may potentiate, refine or replace the action of antibiotics without exerting selective pressure for antibiotic resistance. They are a heterogeneous group of molecules that are similar in that they act by interfering with a mechanism the bacteria use to decrease their susceptibility to antibiotics; by reducing the microorganism's virulence; or by rendering the germ more susceptible to the host immune system. Such agents include: quorum sensing inhibitors; agents that interfere with biofilm construction (the sugars fucose and galactose, and novel dendrimers acting on lectin blockade); efflux pump inhibitors that stop bacteria removing antibiotics from within the bacterial cell; glutamine as an amino acid supplement; and biological agents (such as bacteriophages) that infect bacteria causing their break-down and demise. In the case of bacteriophages that may cause the death of the organism, they act by 'infecting' the bacteria and therefore act differently to, but alongside, conventional antibiotics.

Issues

1. To determine whether the use of elective (regular) IV antibiotics compared with symptomatic IV antibiotics is associated with an improvement in clinical status and survival rates in CF patients.
2. To assess whether oral anti-pseudomonal antibiotics both as a treatment for pulmonary exacerbations and as a long-term treatment in chronic infection is associated with an improvement in clinical status and survival rates in people with CF.
3. To recognize any adverse effects associated with the use of elective IV antibiotics.
4. To detect whether the use of elective IV antibiotics leads to an increase in the development of resistant organisms.
5. To determine if antibiotic adjuvant therapies improve clinical and microbiological outcome of pulmonary infection in people with CF.
6. To evaluate the use of bronchoscopy-guided antimicrobial therapy in the management of lung infection in adults and children with cystic fibrosis.

What is known

4 CDSR evaluated these topics, one studying elective versus symptomatic IV antibiotic therapy, another evaluating the role of oral antibiotic therapy, the third determining if antibiotic adjuvant therapies improve clinical and microbiological outcome of pulmonary infection in people with CF and the last searching evidence to support the routine use of bronchoalveolar lavage for the diagnosis and management of pulmonary infection in subjects with CF.

No conclusive evidence is available that an elective regimen of IV antibiotics is more effective than a symptomatic regimen in maintaining respiratory function in CF (Breen L, 2012). Neither is there statistically significant evidence to suggest that an elective regimen was harmful encouraging the formation of antibiotic resistant micro-organisms and consequently increased mortality.

It should be noted that the total number of participants in well conducted RCT was small and that all studies were conducted in patients with chronic PA infection; more general conclusion on the treatment of chronic infection in CF are not possible.

A CDSR (Horsley A, 2016) assessed the effectiveness and safety of different antibiotic regimens in people with CF experiencing an exacerbation and chronically infected with organisms of the *Burkholderia cepacia* complex (BCC). No conclusions can be drawn from this review. Clinicians must continue to assess each person individually, taking into account *in vitro* antibiotic susceptibility data,

previous clinical responses and their own experience. Another CDSR (Frost F, 2021) assessed the effects of long-term oral and inhaled antibiotic therapy targeted against chronic BCC lung infections in people with CF. Unfortunately, insufficient evidence from the literature was found to determine an effective strategy for antibiotic therapy for treating chronic BCC infection.

Another CDSR (Remmington T, 2016) showed that no evidence is available from RCTs that oral anti-pseudomonal antibiotics, alone or in combination with another therapy, are any more or less effective in treating acute pulmonary infectious exacerbations or for long-term treatment of chronic infection in people with CF than other therapies.

There is no evidence that the use of adjuvant therapies may prove a beneficial alternative to conventional antibiotics alone in the treatment of pulmonary infection in CF people (Hurley MN, 2020).

In particular, neither beta-carotene or garlic showed a significant improvement in clinical state or the number of infections. One study of zinc supplementation showed fewer oral antibiotics were needed, but the same was not true for intravenous antibiotics (Abdulhamid I, 2008). A more recent double-blind randomized placebo-controlled trial was conducted among children with CF to assess the effect of zinc supplementation (30 mg/day) on the need for antibiotics and pulmonary function tests (Sharma G, 2016). The study did not show any significant difference in the need forantibiotics, pulmonary function tests, hospitalization, colonization with Pseudomonas, or the need for antibiotics.

Emerging data suggests a possible role for cysteamine as an adjunct treatment for pulmonary exacerbations of cystic fibrosis (CF) that continue to be a major clinical challenge. A multicentre double-blind randomized clinical trial was performed in adults with CF experiencing a pulmonary exacerbation, being treated with standard care that included aminoglycoside therapy. They were randomized equally to a concomitant 14-day course of placebo, or one of 5 dosing regimens of cysteamine. Cysteamine had no significant effect on sputum bacterial load, however technical difficulties limited interpretation. The most consistent findings were for cysteamine 450mg twice daily that had effects additional to that observed with placebo, with improved symptoms, CRISS additional 9.85 points (95% CI 0.02, 19.7) p = 0.05, reduced blood leukocyte count by 2.46x109 /l (95% CI 0.11, 4.80), p = 0.041 and reduced CRP by geometric mean 2.57 nmol/l (95% CI 0.15, 0.99), p = 0.049.

Another point of view could be the evaluation of adjunctive therapies to the antibiotic treatment of a pulmonary exacerbation. In particular, US authors studied whether adjunctive systemic corticosteroid therapy is associated with improved outcomes in acute CF PEx. Performing a secondary analysis of STOP2, a large multicenter RCT of antimicrobial treatment durations for adult PWCF presenting with PEx, this study showed that empiric, physician-directed treatment with systemic corticosteroids, while common, is not associated with improved clinical outcomes in PWCF receiving antibiotics for PEx (McElvaney OJ, 2024).

To determine whether adjuvant oral prednisone treatment would improve recovery of forced expiratory volume in 1 second ($ppFEV_1$) in CF PExs not responding to antibiotic therapy, a randomized, double-blind, placebo-controlled trial in pwCF treated with intravenous (IV) antibiotics for a PEx was performed. At Day 7, those who had not returned to >90% baseline $ppFEV_1$ were randomized to adjuvant prednisone 1 $mg \cdot kg^{-1}$ twice daily (max 60 mg/day) or placebo for 7 days. The primary outcome was the difference in proportion of subjects who recovered >90% baseline $ppFEV_1$ at Day 14 of IV antibiotic therapy. This study failed to detect a difference in $ppFEV_1$ recovery between adjuvant oral prednisone and placebo treatment in pwCF not responding at day 7 of IV antibiotic therapy for PExs (Waters V, 2024

Finally, there is no clear evidence to support the routine use of bronchoalveolar lavage for the diagnosis and management of pulmonary infection in pre-school children with cystic fibrosis compared to the standard practice of providing treatment based on results of oropharyngeal culture and clinical symptoms. No evidence is available for adult and adolescent populations (Jain K, 2018).

Unresolved questions

There have been insufficient RCTs of elective versus symptomatic administration of intravenous antibiotics in people with CF to answer important questions about long-term outcomes.

Studies should be carried out to evaluate the effectiveness of routine elective IV antibiotics on long-term lung function, adverse effects and mortality in people with CF. The most widely used elective regimen is that of three-monthly administration and this should be compared with standard symptomatic IV treatment in a multicentre, adequately-powered and well-designed RCT to address these important issues.

Future trials should also be designed to adequately compare oral treatment with current standard therapies for both acute pulmonary exacerbations and long-term treatment of chronic infection.

No RCT is available about patients chronically infected with microorganisms different from PA. It could be of interest to evaluate the best choice for treatment of germs other than PA.

New strategies aiming to antibiotic adjuvant therapies should be founded on robust *in vitro* pre-clinical development work including models of bacterial infection considering both planktonic and biofilm modes of growth. Well-designed RCTs are required to determine the efficacy of any new strategy. Recent studies have found an association between vitamin D status and risk of PE in children and adults with CF. The ongoing “Vitamin D for enhancing the Immune System in Cystic fibrosis (DISC) study” is a multi-center, double-blind, randomized, placebo-controlled trial that will test the hypothesis of whether high dose vitamin D given as a single oral bolus of 250,000 IU to adults with CF during a PE followed by a maintenance dose of vitamin D will improve time to next PE and re-hospitalization, improve survival and lung function compared to placebo and reduce the rates of PE (for a description of the study see

Tangpricha V, 2017).

Keywords

Bacterial Infections; Burkholderia cepacia; Colonization; Exacerbation; Haemophilus influenzae; Infection; Pneumonia; Pseudomonas

aeruginosa; Respiratory Tract Infections; Staphylococcus aureus; Stenotrophomonas Maltophilia; Aminoglycosides; Anti-Bacterial Agents; Carbapenems; Cephalosporins; Macrolides; Monobactams; Others anti-bacterial agents; Penicillins; Quinolones; Tetracyclines;