Antibiotics for prevention of respiratory exacerbations

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

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Background

The treatment of chronic infection in cystic fibrosis (CF) aims to preserve lung function, improve quality of life, and reduce mortality. However, there is no international consensus on the optimal management of chronic infection in people with CF.

Two main strategies are widely practiced. The elective regimen involves the administration of regular courses of intravenous (IV) antibiotics, usually every three months, irrespective of clinical status. The alternative approach is a symptomatic regimen, consisting of prompt treatment of acute exacerbations based on clinical or radiological findings or deterioration in lung function parameters.

An additional strategy that has been considered is the use of oral antibiotic therapy.

Most attention in the treatment of chronic infection has focused on *Pseudomonas aeruginosa* (PA). However, other microorganisms are also relevant in the assessment of chronic CF lung disease, including *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia* , methicillin-susceptible *Staphylococcus aureus* (MSSA), and methicillin-resistant *S. aureus* (MRSA). Recent reviews and updates on antimicrobial therapy in CF are available (Waters V. et al 2015)(Epps QJ, 2020)(Magréault S, 2021)(Green HD).

An area of growing interest, closely related to the intensive use of antibiotics in CF, is the role of antibiotic adjuvant therapies. These agents may potentiate, refine, or partially replace the activity of antibiotics without exerting selective pressure for antimicrobial resistance. Although heterogeneous, they share common mechanisms, including interference with bacterial processes that reduce antibiotic susceptibility, attenuation of microbial virulence, or enhancement of host immune clearance. Such agents include quorum-sensing inhibitors; compounds that disrupt biofilm formation (e.g., the sugars fucose and galactose, and novel dendrimers targeting lectin blockade); efflux pump inhibitors that prevent bacterial extrusion of antibiotics; glutamine as an amino acid supplement; and biological agents such as bacteriophages.

Bacteriophages, which can directly cause bacterial death, act by infecting bacteria and therefore function differently from, but potentially synergistically with, conventional antibiotics. Phages are viruses with high strain specificity that infect bacteria. Lytic phages hijack bacterial cellular machinery to replicate and ultimately lyse the host cell, releasing progeny phages that initiate further infection cycles. Because their bactericidal mechanism is distinct from that of antibiotics, bacteriophages represent a promising strategy for targeting antibiotic-resistant pathogens.

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.
7. To explore pharmacokinetics, efficacy and safety of novel phage-based therapeutics in antibiotic-resistant pulmonary bacterial infections by PA.

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.

A recent study study aimed to determine whether broader-spectrum antibiotics were associated with improved clinical outcomes compared to narrower-spectrum antibiotics for PEx treatment (Somajayi R, 2025). The conclusion of the study is that opportunities exist to select narrower-spectrum antibiotics for PEx treatment in CF to minimize the risks of antibiotic toxicities.

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).

A recent RCT described the development of a three-phage cocktail (BX004-A) designed to target a wide range of *P. aeruginosa* strains. In Part 1 of a first-in-human, double-blind, placebo-controlled phase 1b/2a trial (NCT05010577), the authors evaluated BX004-A in nine adults with CF chronically infected with *Pseudomonas aeruginosa*. BX004-A met its primary safety and tolerability endpoints. Exploratory outcomes included pharmacokinetics and changes in *P. aeruginosa* sputum density. Efficient phage delivery to the lower airways was achieved, with a possible reduction in sputum bacterial burden observed in the treatment group. However, the small sample size limits conclusions on efficacy. These findings support continued development of phage-based therapies for antibiotic-resistant pulmonary infections.

Unresolved questions

Revised version (grammar and fluency, academic tone):

There have been insufficient randomized controlled trials (RCTs) comparing elective and symptomatic administration of intravenous antibiotics in people with CF to address key questions regarding long-term outcomes.

Further studies are needed to evaluate the impact of routine elective IV antibiotic therapy on long-term lung function, adverse effects, and mortality in people with CF. The most commonly used elective regimen—three-monthly IV antibiotic administration—should be compared with standard symptomatic IV treatment in a multicenter, adequately powered, well-designed RCT to address these issues.

Future trials should also be designed to rigorously compare oral antibiotic therapy with current standard treatments for both acute

pulmonary exacerbations and the long-term management of chronic infection.

To date, no RCTs have specifically addressed patients chronically infected with pathogens other than *Pseudomonas aeruginosa*. Evaluating optimal treatment strategies for microorganisms other than PA therefore represents an important unmet need.

New approaches involving antibiotic adjuvant therapies should be grounded in robust preclinical in vitro development, including bacterial infection models that account for both planktonic and biofilm growth. Well-designed RCTs are subsequently required to determine the clinical efficacy of these strategies. In this context, recent studies have reported an association between vitamin D status and the risk of pulmonary exacerbations in children and adults with CF. The ongoing *Vitamin D for Enhancing the Immune System in Cystic Fibrosis* (DISC) study is a multicenter, double-blind, randomized, placebo-controlled trial designed to test whether a single high-dose oral bolus of vitamin D (250,000 IU) administered during a pulmonary exacerbation, followed by maintenance therapy, improves time to the next exacerbation and re-hospitalization, as well as survival and lung function, compared with placebo, and reduces exacerbation rates (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;