Antibiotics for prevention of respiratory exacerbations

Antibiotic treatment of early pseudomonas aeruginosa

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Background

The chronic presence of Pseudomonas aeruginosa (PA) in respiratory secretions is a major predictor of morbidity and mortality in children with CF. The first PA colonization episode can occur very early in life. After a first ever colonization episode, patients may go through different episodes of colonization (intermittent colonization), preceding chronic colonization by months to years, eventually resulting in chronic infection. PA strains causing early colonization have usually a non-mucoid phenotype, whereas PA strains in chronically colonized patients are mucoid and form biofilms. While the emergence of chronic and mucoid Pseudomonas aeruginosa (Pa) infection are both associated with poorer outcomes among CF patients, their relationship is poorly understood. US researchers, evaluating data from the CFF registry, examined the longitudinal relationship of incident, chronic and mucoid Pa in a contemporary, young CF cohort in the current era of Pa eradication therapy (Heltshe SL, 2018). Finally, the negative impact of airway inflammation linked to Pa infection has been showed to be severe and persistant also following successful P. aeruginosa eradication and is significantly associated with bronchiectasis progression. In this view, prevention measures and prompt identification of early Pa infection are both mandatory together with anti-inflammatory treatments (Garratt LW, 2021).

PA strains causing early infection are usually antibiotic sensitive and have low bacterial density in the airways. As a result, the treatment strategy has shifted from suppressive therapy in patients chronically colonized by PA to attempts at early eradication therapy as soon as PA is detected. A review on this topic was published (Schelstraete P, 2013).

Reviews on the role, the pathophysiology and the therapeutic approach of PA infection in people with CF have been also published (Talwakar JS, 2016 and Lund-Palau H, 2016)

There are differences in the approach to detection and management of early P. aeruginosa infection. Some CF centres advocate frequent microbiological surveillance with attempts to eradicate PA when it first appears in the lung whereas others treat only when clinical or radiological signs of pulmonary infection are present. There is evidence that, when PA is cleared from respiratory secretions it is not simply suppressed because, when infection recurs, this is with a genetically distinct organism in most cases.

A consensus document (Döring G, 2012), considering that a risk/benefit ratio favors antibiotic eradication therapy (AET), suggests to initiate AET as soon as possible after a positive *Pa* respiratory culture, although there is currently no specific treatment strategy for the eradication of *PA* that has been recommended. However, the current data suggest that: "*28 days of Tobramycin Inhaled Solution, when there is a positive culture, is a recommended treatment strategy for the purpose of eradication of P. aeruginosa. However, because a number of treatment protocols have been shown to be of similar effectiveness including oral, inhalation and intravenous therapy, and there are only few comparative studies available, the optimal antibiotic regimen is not known*."

The US CF Foundation strongly recommends, in its guidelines (Mogayzel PJ, 2014), inhaled antibiotic therapy for the treatment of initial or new growth of PA from an airway culture, stating that the favored antibiotic regimen is inhaled tobramycin (300 mgtwice daily) for 28 days.

While antibiotic eradication therapy (AET) of early Pseudomonas aeruginosa infection is considered standard of care, its long-term effect on the subsequent course of cystic fibrosis (CF) lung disease remains unclear.A single-center study from the CF Centre of Toronto (Canada) demonstrated for the first time that successful *P. aeruginosa* eradication therapy is associated with improved long term lung function, supporting the current standard of care in the management of CF patients. Thus, AET can not only result in improved microbiological outcomes, but clinical outcomes as well (Casaredi IG, 2023).

Finally, another possible approach to the prevention of PA infection could be represented by vaccines and it is important to know whether vaccination against PA can prevent lung infection.

In a recent review, several of the clinical trials, specifically designed to combat *P. aeruginosa* infections in CF patients, patients with *P. aeruginosa* VAP, and *P. aeruginosa*-infected burn patients were examined (Elmassry MM, 2023).

Issues

- It is uncertain whether eradication strategies result in increased survival or improved quality of life for people with CF.
- It is uncertain which eradication strategies result in successful eradication of early PA infection.
- The cost-effectiveness of these strategies remains undetermined.
- While Pseudomonas aeruginosa (Pa) eradication regimens have contributed to a decline in Pa prevalence in people with cystic fibrosis (CF), this antibiotic exposure might increase the risk of acquisition of drug-resistant organisms.
- The effectiveness of vaccination against*PA* in cystic fibrosis.
- The potential correlation between paranasal sinus and lower airway bacteriology.

What is known

One CDSR review examined this issue (Langton Hewer SC, 2023). It identified eleven eligible trials of antibiotic strategies for the eradication of P. aeruginosa infection in CF, with data from 1449 participants. The authors found that nebulised antibiotics, alone or with oral antibiotics, were better than no treatment for early infection with P aeruginosa. Eradication may be sustained in the short term. There is insufficient evidence to determine whether these antibiotic strategies decrease mortality or morbidity, improve quality of life, or are associated with adverse effects compared to placebo or standard treatment. Four trials comparing two active treatments have failed to show differences in rates of eradication of P aeruginosa. One large trial showed that intravenous ceftazidime with tobramycin is not superior to oral ciprofloxacin when inhaled antibiotics are also used. There is still insufficient evidence to state which antibiotic strategy should be used for the eradication of early P aeruginosa infection in CF, but there is now evidence that intravenous therapy is not superior to oral antibiotics.

A recent CDSR review examined strategies to delay the time to PA recurrence in people with CF (Palser S, 2019). The authors evaluated the medical literature to establish whether secondary prevention strategies, using antibiotics or other therapies, increase the chances of people with CF remaining free from PA infection following successful eradication therapy. The main conclusion is that cycled TIS therapy may be beneficial in prolonging the time to recurrence of PA after successful eradication, but further trials are required, specifically addressing this question and in both adults and children.

One single-arm, open-label study was conducted to evaluate the safety and efficacy of a 28-day treatment course of Aztreonam Lysine (AZLI) to eradicate newly acquired PA infection in pediatric CF patients (Tiddens HAWM, 2015). The study showed that AZLI was effective and well tolerated in eradicating PA from newly infected pediatric patients with CF. These eradication rates were consistent with success rates reported in the literature for various antibiotic regimens, including other inhaled antibiotics studied for eradication.

Canadian authors (Blanchard AC, 2017) provided a multi-step eradication protocol. This study, although retrospective and limited to the experience of a single center, is however very interesting, trying to optimize the eradication strategy by a multi-step approach. The study is accompanied by an editorial (Cogen J, 2017), that examines and evaluates the issue of the PA eradication.

Recently, a double-blind, placebo-controlled trial randomised CF patients <7?years (N?=?51) with early Pa-infection to tobramycin inhalation solution (TOBI 300?mg) or placebo (twice daily) for 28?days with an optional cross-over on Day 35. Primary endpoint was proportion of patients having throat swabs/sputum free of Pa on Day 29 (Ratjen F, 2019). The authors conclude that TOBI was effective in eradicating early Pa-infection (on Day 29, 84.6% patients in the TOBI versus 24.0% in the placebo group were Pa-free) with a favourable safety profile in young CF patients.

One retrospective study in 2020 observed that the eradication rate for PA in clinical practice is similar to that published in the literature (Jablonski L, 2020). Consistent with published guidelines, these microbiologic outcomes do not support the addition of an oral FQ to TIS for initial PA eradication.

One retrospective study examined the effectiveness of inhaled tobramycin in early eradication of *P aeruginosa* in infants (younger than 1 year of age) with CF (Choi J, 2020). Of 18 patients included in the study, 9 received inhaled tobramycin and an oral fluoroquinolone and 9 received inhaled tobramycin alone. Microbiologic clearance of respiratory cultures was observed in 83% patients at end of therapy and 78% of patients at 1 month posttherapy. Eradication of *P aeruginosa* was observed in 56% of patients at 6 months posttreatment with sustained culture negativity observed in 39% of patients up to 18 months.

Recently were published the results of a trial (**TORPEDO-CF**) that compared the effectiveness and safety of 14-days intravenous ceftazidime and tobramycin versus 12-weeks oral ciprofloxacin, both combined with 12 weeks inhaled colistimethate sodium, in the eradication of PA. Compared with oral therapy, intravenous antibiotics did not achieve sustained eradication of PA in a greater proportion of patients with CF, and was more expensive. Although there were fewer hospitalisations in the intravenous group than the oral group during follow-up, this confers no advantage over oral treatment because intravenous eradication frequently requires hospitalisation. These results do not support the use of intravenous antibiotics to eradicate PA in CF (Langton Hewer SC, 2020). The TORPEDO-CF study was also evaluated by an HTA (Langton Hewer SC, 2021)

Similar conclusion was obtained by a retrospective observational cohort study aiming to compare the effectiveness of intravenous therapy versus inhalation with/without oral therapy in the eradication of new-onset P aeruginosa. This study observed no advantage of intravenous therapy compared to inhalation therapy in terms of eradication success (Sunman B, 2022).

Several economic evaluation were available (Baumann U, 2003; Iles R, 2003). They agree that the implementation of early eradication treatment, decreasing the prevalence of patients chronically infected by PA, might bring a notable decrease in costs by means of the reduction in hospital attendance and intravenous (IV) antibiotic administration, which would be expected to improve the patients' quality of life and reduce interference to schooling and work. Use of TNS would reduce the use of health care services, particularly hospital days, and lead to substantial savings in direct medical costs that would offset its acquisition price.

Another CDSR review (Krogh Johansen H, 2015) aimed to study whether vaccination against PA is beneficial in CF, and to compare the effects of different vaccines. The results of the three trials included in the review did not suggest that the vaccines tested for preventing infection against *P. aeruginosa* were effective.

Significantly more children with CF show clearance of PA from their respiratory secretions two months after commencing antibiotic therapy aimed at eradication of the organism from their lower respiratory tract when compared to placebo. This effect may last for several months. No improvement in clinical outcome measures following treatment was shown. However, the small numbers of participants in the eligible trials could mean that statistical power to detect changes in clinical outcomes was insufficient. There was no significant difference in the rate of common adverse effects nor in the isolation of micro-organisms other than PA.

The aim of antibiotic therapy for early PA infection in CF should be both eradication of the micro-organism and improvement in (or slowing in the rate of decline of) clinical parameters, whilst minimising adverse effects and the isolation of new micro-organisms. While Pseudomonas aeruginosa (Pa) eradication regimens have contributed to a decline in Pa prevalence in people with CF, this antibiotic exposure might increase the risk of acquisition of drug-resistant organisms. Recently, a study evaluated the association between antipseudomonal antibiotic exposure intensity and acquisition risk of drug-resistant organisms among children with CF and new Pa infection. Among 249 participants, there was no increased acquisition risk of any organism associated with greater inhaled antibiotic exposure. With each additional week of oral antibiotics, there was an increased hazard of Achromobacter xylosoxidans acquisition (HR,

1.24; 95% CI: 1.02-1.50; P = .03). Treatment with intravenous antibiotics was associated with an increased hazard of acquisition of multidrug-resistant Pa (HR, 2.47; 95% CI: 1.28-4.78; P = .01) and MRSA (HR, 1.57; 95% CI: 1.03-2.40; P = .04). In conclusion, results from this study illustrate the importance of making careful antibiotic choices to balance the benefits of antibiotics in people with CF while minimizing risk of acquisition of drug-resistant organisms (Cogen JD, 2021).

US researchers tested the hypothesis that the addition of azithromycin to tobramycin inhalation solution in children with CF and early Pa decreases the risk of pulmonary exacerbation and prolongs the time to Pa recurrence (Mayer-Hamblett N, 2018). Azithromycin was associated with a significant reduction in the risk of pulmonary exacerbation and a sustained improvement in weight, but had no impact on microbiological outcomes in children with early Pa.

All results should be interpreted with caution. Reporting of the presence of organisms in respiratory secretions is difficult to standardise, dependent on the sampling methods used and on the number of samples taken. The trials used a heterogeneous mix of methods to sample respiratory secretions from both the lower and upper respiratory tracts.

Overall, there is insufficient evidence to state which antibiotic strategy should be used for the eradication of early PA infection in CF.

German authors compared three different antibiotic eradication regimens in pediatric CF: an administration according to a standard-operating procedure (SOP) order vs. administration outside of this order (ooSOP). This observational study includes all CF patients<18 years who received one of three Pa eradication treatments in the past eight years at our center: 1) inhaled high-dose tobramycin (Hi-TOBI), 2) inhaled colistin+oral ciprofloxacin (COL/Cip), 3) inhaled low-dose tobramycin+4 intravenous 14-day Pa active antibiotic treatments (lo-Tobra/IV). Eradication rates of the three treatment regimens performed according to the SOP-based order vs. ooSOP were compared. Performed according to SOP order, Hi-TOBI showed the greatest efficacy, followed by lo-Tobra/IV and finally COL/Cip, while ooSOP lo-Tobra/IV was most successful, followed by COL/Cip and Hi-TOBI. Previous Pa-infections and Pa-therapies along with age at CF diagnosis were risk factors for eradication failure. In conclusion Antibiotic treatment in SOP-based pre-defined order leads to significantly better eradication rates than individual modifications of the order of administration. A short course of inhalational high-dose Tobramycin is most successful at the first attempt. Prolonged antibiotic therapy seems to improve eradication after failed initial attempts. (Schütz K, 2023)

Recently, ALPINE2 (a double-blind, phase 3b study) compared the efficacy and safety of a shortened 14-day course of aztreonam for inhalation solution (AZLI) with 28-day AZLI in paediatric pwCF with the aim of the eradication therapies for newly isolated PA. Non-inferiority of 14-day AZLI versus 28-day AZLI *was not demonstrated*. Both courses were well tolerated, further supporting AZLI short-term safety in paediatric and adolescent pwCF (Gilchrist FJ, 2023).

Recently, several studies provide support to the hypothesis that paranasal sinuses are potential areas for bacteria growth and evolution before infecting the lower airways in CF patients. Limited evidence exists to suggest optimum treatment methods in the eradication of microorganisms in the paranasal sinus of CF patients (Wilson P, 2014).

Unresolved questions

There is an urgent need for trials, which are specifically designed to examine the hypothesis that antibiotic treatment of early PA infection will prevent or delay chronic infection, and result in appreciable clinical benefit to patients, without causing them harm. An observational study (Mayer-Hamblett N, 2015), based on the follow up data of the EPIC trial, showed no association between eradication status and clinical outcomes including the rate of exacerbations and lung function decline.

Eradication treatment is part of routine clinical practice in many CF centres and clinical trials comparing alternative eradication regimens may be preferable for pragmatic or ethical reasons.

Consideration should be given to appropriate outcome measures particularly spirometric lung function, nutritional status, socio-economic outcomes including quality of life and duration of follow up.

Long-term follow-up trials with careful clinical and bacteriological surveillance are required.

Additional basic research is needed to further increase our understanding of those elements of the immune response to PA that could potentially have a protective effect.

The influence of the upper airways on the general health of CF patients has been the object of investigation to verify the hypothesis that sinonasal involvement may function as a reservoir for pulmonary infection and influence the results of eradication strategies.

A further review provide an overview of the changing perceptions of *P. aeruginosa* infection management, including considerations on detection and treatment, the therapy burden associated with inhaled antibiotics and the potential effects of CFTRm on the lung microbiome. The authors conclude that updated guidance is required on the diagnosis and management of *P. aeruginosa* infection. In particular, they highlight a need for prospective studies to evaluate the consequences of stopping inhaled antibiotic therapy in pwCF who have chronic *P. aeruginosa* infection and are receiving CFTRm. This will help inform new guidelines on the use of antibiotics alongside CFTRm (Burgel PR, 2024).

Keywords

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