Antibiotics for prevention of respiratory exacerbations

Inhaled antibiotics in cystic fibrosis

Code: 101-102 **Updated:** December 01, 2024

Background

Inhaled antibiotics in cystic fibrosis (CF) have the aim to reduce the bacterial load in the lung, thereby reducing lung damage and the rate of deterioration of lung function and frequency of exacerbations of infection. These outcomes should be associated with improvement in quality of life and in survival.

Additional issues of relevance around the use of inhaled antibiotics in CF include financial cost, increased time of treatment, risks of adverse effects of the drugs and an increase in the likelihood of acquisition of drug-resistant organisms by long-term exposure to antibiotics. A review of approved and developing aerosol antibiotics was available by Doring G et al. A further update on this topic was published by Tai GTP et al.

In preparation for an FDA-sponsored workshop held on June 27, 2018 to consider the clinical development of new inhaled antibiotics for people with CF and non-CF bronchiectasis, a group of CF investigators met to outline key considerations for CF inhaled antibiotic development. (Nichols DP, 2019)

Recently, the paranasal sinuses are considered an important niche for the colonizing bacteria in many CF patients. The paranasal sinuses often harbor distinct bacterial subpopulations, and in the early colonization phases there seems to be a migration from the sinuses to the lower airways, suggesting that independent adaptation and evolution take place in the sinuses. Inhaled antibiotics could be relevant to prevent lung colonization.

An important issue is to evaluate how local conditions affect the clinical efficacy of antibiotic aerosol particles after deposition in the airways of patients with CF. In fact, after deposition in the airways, the local efficacy of inhaled antibiotics can be reduced by molecules within CF mucus and the alginate layer surrounding Pseudomonas aeruginosa (PA) (Bos AC, 2017).

Based on the available evidence inhaled antibiotics have been recommended in Cystic Fibrosis Foundation Guidelines (Mogayzel Jr, PJ, 2013) as a standard of treatment for children 6 years and above with mild to severe lung disease and in the standards of care of the European CF Society (Castellani C, 2018 ; Southern KW, 2024).

In spite of these recommendations, the use of inhaled antibiotics is very different in the different countries. In The US, the CFF Patient Registry reports in 2019 that in patients PA+ and ?6 years 68.2% were using inhaled Tobramycin and 43.5% inhaled aztreonam. In Europe, the range of patients using inhaled antibioticsis is very wide, from 55% in the UK, to 47% in Germany and 37% in Italy (European CF registry 2018). In particular, Naehrig S et al. (Naehrig S, 2023) describe the use of inhaled antibiotics in pwCF with intermittent Pseudomonas or without Pseudomonas infection, using data of the German CF Registry. A total of 1960 pwCF had chronic P. aeruginosa infection and were retrospectively evaluated. Almost 90% (n = 1751) received at least one inhaled antibiotic. The most commonly used inhaled antibiotic was colistin solution for inhalation (55.2%), followed by aztreonam solution for inhalation (32.6%) and tobramycin solution for Inhalation (30%). Almost 56% of adults and 44% of children alternated two antibiotics for inhalation. It will be interesting to see how the introduction of the highly effective modulator elexacaftor/tezacaftor/ivacaftor will change the use of inhaled antibiotics.

Finally, the use of CFTR modulators are likely to result in substantial changes in CF airway microbiology. People with CF, their families, and/or their acquaintances ranked airway clearance techniques and inhaled antibiotics as the most burdensome treatments. In the next years the use of inhaled antibiotics could be reconsidered (Elborn JS,2023).
However, it is unclear how improved CFTR activity affects CF lung infections. US authors of the PROMISE-Micro Study Group showed that treatment with the most effective CFTR modulator currently available produced large and rapid reductions in traditional CF pathogens in sputum, but most participants remain infected with the pathogens present before modulator treatment (Nichols D, 2023).

A recent review addresses the current treatment challenges of antibiotic-resistant bacteria in the lung with some clinical outcomes and provides future directions with innovative ideas on new inhaled formulations and delivery technology that promise enhanced killing of antibiotic-resistant biofilm-dwelling bacteria (Islam N, 2024).

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). However, two years after ETI initiation, reductions in the use of several routine therapies were observed in a national cohort of Danish pwCF, with the largest declines in airway medications and antibiotics. These findings highlight ETI's real-world impact beyond conventional clinical metrics (Raket HK, 2024).

A study of data from the US CFF Registry determined the proportion of pwCF with chronic, intermittent or negative Pa infection categories, their clinical and demographic characteristics, factors associated with inhaled antibiotic prescription and changes between 2011 and 2019.

Proportion of pwCF with chronic and intermittent Pa decreased and antibiotic prescription rates increased for these groups and decreased for Pa negative pwCF. Hispanic ethnicity, female sex, pancreatic insufficiency, CF diabetes, and ivacaftor/lumacaftor were

associated with higher antibiotic prescriptions for each Pa status. Among Pa-negative pwCF prescriptions were higher with Burkholderia spp. (1.17, (CI_{95} 1.03,1.34)) or MRSA (OR 1.45, (1.26,1.68)) but decreased between 2011 and 2019. For Aspergillus OR increased to 1.6,(1.3,1.8) in 2019. Prescriptions for pwCF on ivacaftor decreased, becoming lower in 2019 for chronic (OR 0.7, (0.5,0.8)) and Pa-negative pwCF (OR 0.7, (0.5,0.8)). In conclusion, factors predicting inhaled antibiotic prescription differed between 2011 and 2019 indicating changes in health and care for pwCF even prior to triple-modulators. (Muhleback MS, 2024)

Issues

To evaluate if inhaled antibiotic treatment in CF:

1. improves lung function and reduces frequency of pulmonary exacerbations
2. improves nutritional status and quality of life
3. improves survival
4. increases frequency of antibiotic-resistant organisms
5. causes renal or auditory impairment and drug sensitivity reactions
6. improves the treatment of pulmonary exacerbations
7. are effective in subjects **without** chronic PA infection

What is known

The practice of prescribing inhaled antibiotics for many years, used to suppress chronic infection in people with CF, is widespread. The most commonly used drugs at present are tobramycin, colistin, aztreonam lysine and, recently levofloxacin. Others are being developed: amikacin, ciprofloxacin, and combined fosfomycin-tobramycin.

A recent CDSR (Smith S, 2022) evaluated the effects of long-term inhaled antibiotic therapy in people with cystic fibrosis on clinical outcomes (lung function, frequency of exacerbations and nutrition), quality of life and adverse events (including drug sensitivity reactions and survival). The authors concluded that long-term treatment with inhaled anti-pseudomonal antibiotics probably improves lung function and reduces exacerbation rates, but pooled estimates of the level of benefit were very limited. The best evidence available is for inhaled tobramycin. More evidence from trials measuring similar outcomes in the same way is needed to determine a better measure of benefit. Longer-term trials are needed to look at the effect of inhaled antibiotics on quality of life, survival and nutritional outcomes.

Another CDSR assessed the effectiveness, safety, burden of care and adherence to nebulised therapy using the different nebuliser devices available (Daniels T, 2013). The review conclude that clinicians should be aware of the variability in the performance of different nebuliser systems. Technologies such as adaptive aerosol delivery and vibrating mesh technology have advantages over the conventional systems in terms of treatment time, deposition as a percentage of priming dose, patient preference and adherence. There is a need for long-term RCTs of these technologies to determine patient-focused outcomes (such as quality of life and burden of care), safe and effective dosing levels of medications and clinical outcomes (such as hospitalizations and need for antibiotics) and an economic evaluation of their use.

Several recent DARE reviews are available on the topic of this file. A first review (Littlewood KJ, 2012) compared the efficacy of the inhaled antibiotics tobramycin (as solutions and powder), colistimethate sodium (colistin solution) and aztreonam lysine for inhalation (AZLI) based on data from RCT. The authors conclude that all studied antibiotics have comparable efficacies for the treatment of chronic PA lung infection in CF.

Another systematic review (Maiz L, 2013) of the three currently available inhaled antibiotics (aztreonam lysine (AZLI), colistin (COL) and tobramycin (TOB)) was recently published. The review conclude that the choice of treatment for each individual CF patient should be based on the features of the drug (clinical evidence on efficacy and safety), the inhalation system and the patient characteristics.

A further DARE review (Tappenden P, 2013) evaluated the clinical effectiveness and cost-effectiveness of colistimethate sodium dry powder for inhalation (DPI) (Colobreathe(®), Forest Laboratories) and tobramycin DPI (TOBI Podhaler(®), Novartis Pharmaceuticals) for the treatment of Pseudomonas aeruginosa lung infection in CF. The authors conclude that both DPI formulations have been shown to be non-inferior to nebulised tobramycin as measured by FEV1%. However high-quality research concerning the relationship between forced expiratory volume in first second % (FEV1%) predicted or other measures of lung function and survival/health-related quality of life (HRQoL) would be useful.

Long-term treatment with inhaled antibiotics is recommended for people with cystic fibrosis (pwCF) chronically infected with Pseudomonas aeruginosa (PA). However, pwCF without chronic PA infection are also commonly treated with inhaled antibiotics. A registry-based study from the EU evaluated the prevalence and factors associated with inhaled antibiotic treatment in pwCF without chronic PA infection, and long-term outcomes of this treatment. Treatment with inhaled antibiotics was more prevalent with severe genotype, diabetes, pancreatic insufficiency, and past infection with chronic PA (OR 3.8, 95% CI, 2.88-5.04). Treatment with inhaled antibiotics was not associated with a reduced risk for acquisition of PA or other resistant pathogens, or with improved lung function decline, mortality, or transplantation. These findings suggest controlled studies evaluating specific inhaled antibiotic regimens targeting specific pathogens or indications be performed to determine their effect (Orenti A, 2022).

Analysis of single antibiotics

(LIPOSOMAL) AMIKACIN

Liposomal amikacin for inhalation (LAI - Arikace®) comprised of neutral charge liposomes was developed to improve the penetration of the aminoglycoside antibiotic into mucus plugs and *PA* biofilms.

One phase 2 RCT described (Clancy JP, 2013) the safety, tolerability, ef?cacy and pharmacokinetics of four doses of once-daily Arikace for 28 days compared with placebo in CF patients chronically infected with P aeruginosa. The study showed that once-daily Arikace demonstrated acute tolerability, safety, biologic activity and ef?cacy in the short term, supporting phase 3 studies.

One phase 2 randomized, double-blind, placebo-controlled study and an open-label (OL) extension of LAI in patients with refractory nontuberculous mycobacterial lung disease showed that LAI added to a multidrug regimen produced improvements in sputum conversion and 6-minute-walk distance versus placebo with limited systemic toxicity in patients with refractory Mycobacterium abscessus complex (MAC) lung disease (Olivier KN, 2017). A treatment effect was seen predominantly in patients without cystic fibrosis with MAC and was sustained 1 year after LAI. Most adverse events were respiratory, and in some patients it led to drug discontinuation.

A relevant research question is : Does treatment with LAI improve culture conversion in patients with M abscessus pulmonary disease who are treatment naive or who have treatment-refractory disease? In an open-label protocol, patients (30% of the 33 subjects studied had CF) were given LAI (590 mg) added to background multidrug therapy for 12 months. The primary outcome was sputum culture conversion defined as three consecutive monthly sputum cultures showing negative results. The secondary end point included development of amikacin resistance. In this cohort of patients primarily with macrolide-resistant M abscessus, one-half of the patients using LAI showed sputum culture conversion to negative findings. The emergence of mutational amikacin resistance was not uncommon and occurred with the use of clofazimine monotherapy (Siegel SAR, 2023).

One phase 3 study had the purpose to determine whether LAI is effective in treating chronic lung infections caused by Pa in CF subjects (Bilton D, 2020). The effectiveness, safety, and tolerability of LAI was compared to Tobramycin TOBI® (TIS), an inhalation antibiotic already available for use. Cyclical dosing of once-daily LAI was noninferior to cyclical twice-daily TIS in improving lung function. An extension study (ClinicalTrials.gov: NCT01316276; EudraCT: 2011-000443-24) assessed long-term safety, tolerability, and efficacy of LAI in eligible patients who completed the phase 3 study. This study showed that long-term treatment with LAI was well tolerated with a favourable adverse event profile and demonstrated continued antibacterial activity in CF patients with chronic P. aeruginosa infection (Bilton D, 2021).

AZTREONAM LYSINE

Aztreonam is a monobactam antibiotic with excellent coverage of aerobic Gram-negative bacterial species including *PA.* Aztreonam lysine (AZLI) was recently developed in an inhaled formulation to be delivered with a novel and potentially more patient-friendly nebulizer device. Aztreonam is traditionally considered to have strictly Gram-negative coverage, but limited activity may exist for some strains of *Staphylococcus aureus.*

In 2019, 43.5 % of the North American CF subjects in the population older than 6 years with chronic infection by *PA* were on therapy with inhaled AZLI (2019 CFF Patient Registry Report).

CFF Pulmonary Guidelines (Mogayzel PJ Jr, 2013) strongly recommend to use inhaled AZLI for treatment of individuals with CF who are six years of age and older, who have moderate to severe lung disease and with persistent P. aeruginosa infection, to improve lung function and quality of life. Moreover, for individuals with CF, 6 years of age and older, with mild lung disease and P. aeruginosa persistently present in cultures of the airways, the guidelines recommend the chronic use of inhaled AZLI to improve lung function and quality of life.

Among the main clinical studies, (Wainwright CE, 2011) regarded CF patients with mild lung disease, where AZLI-treated patients preserved lung function and suppressed *PA* compared with placebo. Later, (Assael BM, 2013) was an open-label, randomized, parallel-group, active-comparator study, where AZLI demonstrated statistical superiority in lung function and a reduction in acute pulmonary exacerbations compared to Tobramycin Nebulized Solution over 3 treatment courses.

One RCT (Tullis DE, 2014), evaluating the effect of 24 weeks of continuous AZLI treatment on CF patients with chronic infection by Burkholderia Cepacia did not significantly improve lung function.

One single-arm open label study showed that AZLI was effective and well tolerated in eradicating PA from newly infected pediatric patients with CF (Tiddens HAWM, 2015). 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).

Another RCT (Flume PA, 2016) studied if the effect of using a Continuous Alternating Therapy (CAT) regimen of 2 antibiotics of different classes with different mechanisms of action [AZLI and Tobramycin (TIS)] may provide clinical benefits compared to the classic on-off regimen with TIS. AZLI/TIS treatment reduced exacerbation rates by 25.7% (p=0.25; primary endpoint) and rates of respiratory hospitalizations by 35.8% compared with placebo/TIS (p=0.14). AZLI/TIS CAT therapy was well tolerated.

An open-label randomised crossover study explored the clinical and microbiological outcomes associated with substituting inhaled aztreonam lysine (AZLI) for an intravenous antibiotic in the treatment of acute pulmonary exacerbations of CF. This study showed that in adults with CF and P. aeruginosa infection experiencing an acute pulmonary exacerbation, AZLI+IV improved lung function and quality of life compared to the current standard (only IV antibiotics) treatment (Frost F, 2021).

A retrospective observational study was conducted on Spanish patients with CF and chronic *P. aeruginosa* infection who received AZLI between July 2012 and September 2018. AZLI achieved stabilisation of lung function measured by FEV_1 in patients with CF and chronic

P. aeruginosa infection, along with an adequate safety profile (Jimenez-Lozano I, 2023).

CIPROFLOXACIN DPI

Ciprofloxacin (CFX) is a fluoroquinolone antibiotic with potent activity against *PA*. A dry powder for inhalation was developed and is under evaluation for efficacy and safety in CF patients with *PA* chronic infection.

One phase IIb RCT (Dorkin HL, 2015) showed no significant differences in change in FEV1 between ciprofloxacin DPI and the

corresponding placebo group for either dose (p=0.154). However, in pooled analyses, FEV1 decline from baseline to treatment end was significantly lower with ciprofloxacin DPI than with placebo (pooled data; p=0.02). CFX DPI showed positive effects on sputum bacterial load and quality of life, but these effects were not maintained at the 4-week follow-up. CFX DPI was well tolerated and there were no significant differences in type/incidence of treatment-emergent adverse events by treatment group (p=0.115).

A recent review underscores the importance of CFX inhalable formulations against lower respiratory tract infections in preclinical and clinical sectors, their challenges, recent advancements, and future perspectives. (Panthi VK, 2024).

COLISTIN

Colistin is a cationic polypeptide, acting by disrupting the integrity of the bacterial cell membrane. Inhaled colistin has been used in P. aeruginosa-related CF therapy in Europe for decades, although no randomized, placebo-controlled trials have been conducted which favor its use.

In 2019, a median of 9.1 % of the North American CF centers recommend inhaled colistin chronically in the population over 6 years of age (2019 CFF Patient Registry Report).

Surprisingly, there is no adequate RCT evidence to support the long-term use of colistin. Two trials with few participants compared colistin to placebo were not able to be evaluated for efficacy analysis.

Of note, the results obtained from a recent observational comparative cohort study using data from
the UK Cystic Fibrosis Registry (UKCFR) from 2014 to 2018, in a real-world setting of CF patients aged 6 years or older treated with colistimethate sodium dry powder, showed that the safety profile of inhaled colistin was similar to that of other inhaled anti-pseudomonal antibiotics (Kaplan S, 2021).

Tobramycin versus colistin

One study compared tobramycin (300 mg of preservative free solution twice daily) versus colistin (1 million units twice daily) (Hodson ME, 2002), with improvement of FEV1 in the tobramycin group but not in the colistin group, with similar profile of safety.

Another study (Schuster A, 2012) assessed efficacy and safety of a new dry powder formulation of inhaled colistimethate sodium (CDPI) in CF patients aged ?6?years with chronic *PA* lung infection compared to tobramycin inhaled solution (TIS). CDPI demonstrated efficacy by virtue of non-inferiority to TIS in lung function after 24?weeks of treatment and was well tolerated. Recently, CDPI use in CF was reviewed (Conole D, 2014)

LEVOFLOXACIN

Levofloxacin is a fluoroquinolone antibiotic with potent activity against *PA*. It inhibits bacterial
DNA gyrase and topoisomerase IV, thus, blocking bacterial cell growth. Interestingly, levofloxacin's activity is not reduced in CF sputum and, in addition, levofloxacin has antimicrobial activity in biofilms produced by *PA.* MP-376 is a novel solution formulation of levofloxacin for aerosol administration (LIS), developed for the management of CF patients with chronic infections due to *PA.* LIS might also be effective in treating the coinfection of Stenotrophomonas maltophilia and P. aeruginosa (Gajdacs M, 2019).

One RCT (Geller DE, 2011) showed short term (28 days) benefit, in terms of increasing FEV1 and reduction in the need for other anti-*PA* antimicrobials and safety, when LIS was compared with placebo.

Elborn JS et al performed one randomized (2:1), non-inferiority study, comparing LIS and TNS over three 28-days on/off cycles. Non-inferiority was demonstrated (1.86% predicted mean FEV_1 difference [95% CI -0.66; 4.39%]). LIS was well-tolerated, with dysgeusia (taste distortion) as the most frequent adverse event. An open-label extension of this study continued to show favorable efficacy of LIS with no additional safety concerns (Elborn JS, 2016).

A further RCT (Flume PA, 2016) was designed as a multinational, randomized (2:1), double-blinded study of LIS and placebo over 28 days in CF patients ?12years with chronic *PA* infection. Time to exacerbation was the primary endpoint. FEV_1 (% predicted) and patient-reported quality of life were among secondary endpoints. LIS did not demonstrate a difference in time to next exacerbation when compared to placebo. An improvement in FEV_1 (% predicted mean difference 1.31%, p=0.01 [95% CI 0.27; 2.34%]) at 28 days was observed and LIS was well tolerated.

A systematic literature review and Bayesian network meta-analysis (NMA) was conducted to compare the relative short-term (4 weeks) and long-term (24 weeks) outcomes of several inhaled antibiotics versus LIS (Elborn JS, 2016). This review did not provide significant evidence to indicate that the other approved inhaled antibiotics were more effective than LIS for the treatment of chronic *PA* lung infection in patients with CF.

The clinical principles relating to the use of inhaled levofloxacin for the management of *P. aeruginosa* infections in patients with CF has been recently reviewed (Elborn S, 2021).

Finally, a report of RWE showed that inhaled levofloxacin solution has the potential to improve FEV_1 and to reduce the number of bronchopulmonary exacerbations (Schwarz C, 2021).

TOBRAMYCIN

In 2019, 68.2 % of the North American CF population older than 6 years with chronic infection by *PA* used inhaled tobramycin (2019 CFF Patient Registry Report).

CFF pulmonary guidelines strongly recommend to use inhaled tobramycin for treatment of individuals with CF who are six years of age and older, who have moderate to severe lung disease and with persistent P. aeruginosa infection, to improve lung function and quality of life, and reduce exacerbations. Moreover, for individuals with CF, 6 years of age and older, with mild lung disease and P. aeruginosa persistently present in cultures of the airways, the guidelines recommend the chronic use of inhaled tobramycin to reduce exacerbations.

A recent review summarize the available data on tobramycin regarding its molecular characteristics, mechanism of action, and efficacy

and safety for the treatment of acute and chronic P. aeruginosa infection (Schwarz C, 2022)

Eight trials with 1152 participants compared tobramycin to placebo or usual treatment, the duration of the trial varying from 1 month to 33 months. Forty-five per cent of participants were in one high quality trial (Ramsey BW, 1999). Tobramycin was used in a dose of 80 mg, 300 mg and 600 mg, with a frequency of nebulisation of twice daily in six trials and three-times daily in two trials.

Economic evaluation of the use of tobramycin nebuliser solution (TNS) for the treatment of patients moderately severely affected with cystic fibrosis (CF) stated that it lead to reductions 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. The higher cost of TNS treatment was partially offset by other savings. The clinical benefit observed was larger for the sub-group of younger patients.

Tobramycin Inhalation Powder (TIP) was also available for CF patients. Several trials showed a safety and efficacy profile comparable with TIS, but TIP had greater patient satisfaction in all the age groups.

Recently, sinonasal inhalation of vibrating Tobramycin aerosol appears promising for reducing pathogen colonization of paranasal sinuses and for control of symptoms in patients with CF.

An issue to be evaluated is the concomitant use of oral azithromycin and inhaled tobramycin, occurring in approximately half of US CF patients. Recent data suggest that this combination may be antagonistic. In vitro, azithromycin selectively reduced the bactericidal effects of tobramycin in cultures of clinical strains of P. aeruginosa, while up regulating antibiotic resistance through MexXY efflux. A trial from US (Nichols DP, 2017) showed that Azithromycin appears capable of reducing the antimicrobial benefits of tobramycin by inducing adaptive bacterial stress responses in P. aeruginosa, suggesting that these medications together may not be optimal chronic therapy for at least some patients. This hypothesis is also supported by a retrospective cohort study using the U.S. CF Foundation Patient Registry, examining pulmonary outcomes among chronic azithromycin users compared to matched controls over years of use, and consider combined azithromycin use in cohorts using chronic inhaled tobramycin or aztreonam (Nichols DP, 2019).

This question has been recently addressed by a 6-week prospective, randomised, placebo-controlled, double-blind trial testing oral azithromycin versus placebo combined with clinically prescribed inhaled tobramycin in individuals with cystic fibrosis and *P. aeruginosa* airway infection (NCT02677701). Over a 6-week period, including 4 weeks of inhaled tobramycin, the relative change in FEV_1 did not statistically significantly differ between groups (azithromycin (n=56) minus placebo (n=52) difference: 3.44%; 95% CI: -0.48 to 7.35; p=0.085). Differences in secondary clinical outcomes, including patient-reported symptom scores, weight and need for additional antibiotics, did not significantly differ. Among the 29 azithromycin and 35 placebo participants providing paired sputum samples, the 6-week change in *P. aeruginosa* density differed in favour of the placebo group (difference: 0.75 $\log_{10}$ CFU/mL; 95% CI: 0.03 to 1.47; p=0.043). In conclusion, despite having greater reduction in *P. aeruginosa* density, participants randomised to placebo with inhaled tobramycin did not experience significantly greater improvements in lung function or other clinical outcomes compared with those randomised to azithromycin with tobramycin.

Tobramycin versus colistin (see also colistin paragraph)

FOSFOMYCIN/TOBRAMYCIN (FTI)

Fosfomycin/tobramycin for inhalation (FTI), a unique, broad-spectrum antibiotic combination, may have therapeutic potential for patients with CF.

One phase-2 RCT (Trapnell BC, 2012) assessed the effect of FTI vs placebo in the short term (28 days) administration. FTI maintained the substantial improvements in FEV(1) % predicted achieved during the AZLI run-in and was well tolerated. Long term studies on a broader sample of patients are needed to define the potential role of this antibiotic combination.

Unresolved questions

Lung function test results and care with defining exacerbations of respiratory tract infection in terms of hospitalisation and of antibiotic use need more consistent results. Also the effect of long-term use on quality of life and survival needs to be assessed. The level of benefit is uncertain as most trials are small and short, hence uncertainty about any longer-term benefit remains; the optimal dose regimen for several antibiotics is not established as much as no conclusion on the optimum method of aerosol generation and delivery is available; harm of treatment may be underestimated from short-term RCTs, particularly the risk of antibiotic-resistant pathogens emerging with long-term use.

Some specific issues should be investigated:

1. to compare colistin (including different doses) to other antibiotics for benefits and harm, since it is nowadays considered non-ethic the comparison with placebo to determine effectiveness;
2. to determine the optimum dose, daily frequency of administration and frequency of treatment with inhaled antibiotics. Moreover, this therapy was initially approved for intermittent administration. Nowadays the use of continuous inhaled antibiotic regimens of different combinations should be evaluated to define if it may provide additional clinical benefit;
3. to compare antibiotics for benefits and harm; there should be a longer-term comparison of tobramycin and colistin, and perhaps combinations;
4. to determine adverse effects of longer-term use, particularly on the frequency and impact of drug resistance organisms;
5. to explore the role of new available drugs or formulations, moreover evaluating effectiveness as part of an early eradication treatment regimen for CF patients at the initial identification of *PA* infection;
6. to answer the following questions in CF patients experiencing pulmonary exacerbations:

- for mild pulmonary exacerbations, does inhaled antibiotic added to oral antibiotic improve outcomes compared to the oral treatment alone?

- for more severe pulmonary exacerbations, is inhaled antibiotic as effective as the IV formulation of the same drug when either one is added to other IV antibiotics?

7. Most clinical guidelines assume children who have chronic PA infection will continue to isolate PA and therefore stay on anti-PA treatment indefinitely. On the other hand, a proportion of children who are started on long-term inhaled anti-PA treatment for chronic infection subsequently produce PA-negative respiratory samples for a prolonged period of time. When this happens, the only way to find out if the PA has been eradicated or is being supressed by the inhaled antibiotic is the discontinuation of the inhaled treatment and the evaluation of subsequent cultures of respiratory samples.

8. It will be interesting to see how the introduction of the highly effective modulator elexacaftor/tezacaftor/ivacaftor will change the use of inhaled antibiotics (Elborn JS, 2023).

Relatively to the second issue, a double-blind trial compared continuous alternating therapy (CAT) to an intermittent treatment regimen (Flume PA, 2016). Subjects were treated with 3 cycles of 28-days inhaled aztreonam (AZLI) or placebo 3-times daily alternating with 28-days open-label tobramycin inhalation solution (TIS). The results of this trial indicate that AZLI/TIS CAT is well tolerated and may provide additional clinical benefit in CF patients compared with intermittent use of TIS alone. AZLI/TIS treatment reduced exacerbation rates by 25.7% (p=0.25; primary endpoint) and rates of respiratory hospitalizations by 35.8% compared with placebo/TIS (p=0.14). Although the results show a positive trend on the main endpoints, they were statistically not significant, probably because the study was underpowered. Further studies will be needed to better define this issue.

About issue #6, an open-label randomised crossover study explored the clinical and microbiological outcomes associated with substituting inhaled aztreonam lysine (AZLI) for an intravenous antibiotic in the treatment of acute pulmonary exacerbations of CF. This study showed that in adults with CF and P. aeruginosa infection experiencing an acute pulmonary exacerbation, AZLI+IV improved lung function and quality of life compared to the current standard (only IV antibiotics) treatment. These findings support the need for larger definitive trials of inhaled antibiotics in the acute setting (Frost F, 2021).

Recently, a CDSR was published examining if treatment of pulmonary exacerbations with inhaled antibiotics in people with CF improves their quality of life, reduces time off school or work, and improves their long-term lung function (Smith S, 2022). The authors identified only low- or very low-certainty evidence to judge the effectiveness of inhaled antibiotics for the treatment of pulmonary exacerbations in people with CF. The included trials were not sufficiently powered to achieve their goals. Hence, It was not possible to demonstrate whether one treatment was superior to the other or not. Further research is needed to establish whether inhaled tobramycin may be used as an alternative to intravenous tobramycin for some pulmonary exacerbations. To date, inhaled antibiotics have not been meaningfully studied in the context of acute exacerbations as a therapy independent of parenteral antibiotics. Researchers from Israel conducted a real life pilot study to explore the role of dual coverage inhaled antibiotics in the treatment of pulmonary exacerbations in lieu of intravenous antibiotics. Patients were selected for dual inhaled antibiotic treatment if, despite oral antibiotic treatment, they had signs and symptoms of an exacerbation that the attending physician, based on prior clinical experience with the patient, believed would have warranted initiation of intravenous antibiotic therapy. Ten patients met the eligibility criteria and were treated with dual coverage inhaled antibiotics for an exacerbation over a two year period. Eight of ten patients reported improvement in clinical symptoms, primarily decrease in cough, sputum production and shortness of breath. All patients reported adherence with the prescribed inhaled medications, and no adverse side effects were reported by any of the patients. In conclusion, dual coverage intravenous antibiotics can result in recovery from acute non-severe PEx in CF. In acute non-severe PEx, clinicians may consider adding dual coverage inhaled antibiotics to oral antibiotic regimens, before defaulting to intravenous antibiotics. Randomized controlled studies are needed to define the circumstances where dual coverage inhaled antibiotics will be most appropriate for treatment of PEx without the need to resort to IV antibiotics (Heching M, 2024).

About issue #7, a registry-based study from UK, combined with a questionnaire explored if the 29 main pediatric CF centres consider stopping anti-PA treatment in children who are free from PA and if so, after what duration. Responses were received from 23/29 (79%) centres. Of these, 22/23 (96%) stop anti-PA nebs if a child becomes free from PA and all but one, do this after a specific duration of time. This is three years for one centre, two years for eight centres, 18 months for one centre, one year for 10 centres and three months for one centre. The additional criteria children needed to achieve before treatment was stopped varied between centres but included the type and frequency of microbiology samples both before and after stopping, the clinical stability of the patient, PA samples with a mucoid phenotype and adherence to physiotherapy. Given the prevalence of children with chronic infection becoming free from PA, it is unsurprising that the majority (86%) of UK CF centres consider stopping anti-PA nebulised treatment after children are free from PA for between one and two years. However there is no standardised approach for this and rates of PA re-isolation are unknown. There is an urgent need for clinical trials to compare the rates of PA regrowth after inhaled antibiotics are discontinued after different durations of not isolating the organism. The potential benefits from stopping unnecessary inhaled antibiotics are significant with a reduction in cost, treatment burden, side effects and antibiotic resistance (Gilchrist FJ, 2023).

Tobramycin versus colistin: some questions are actually undefined

- to compare colistin (including different doses) to other antibiotics for benefits and harm, since it is nowadays considered non-ethic the comparison with placebo
- there should be a longer-term comparison of tobramycin and colistin, and perhaps combinations as Continuous Alternating Therapy of the two drugs vs single drug on-off treatments

Tobramycin: the following questions are still debating

- to determine the optimum dose, daily frequency and mode of administration, and frequency of treatment with tobramycin;
- to compare antibiotics for benefits and harm; there should be a longer-term comparison of tobramycin and colistin, and perhaps combinations;
- to determine adverse effects of longer-term use, particularly on the frequency and impact of drug resistance organisms.

- The role of TNS as possible unconventional choice instead of intravenous aminoglycosides in the treatment of pulmonary exacerbations. Al Aloul M et al, using a randomized crossover trial design, compared, in a pilot study, 14 days of IV tobramycin with TNS in acute respiratory exacerbations in 20 CF adults chronically infected with *PA*. Patients also received IV colistin in both arms. Improvement in spirometry was similar between the two groups [mean change in FEV_1 % predicted: IV group 16.4 (standard deviation 8.5) versus TNS group 19.9 (11.3), p=0.26], but there was more suppression of sputum *PA* in the TNS group. IV tobramycin was associated with a greater urinary protein leak and higher urinary levels of markers of acute renal tubular injury. This issue needs further studies to be evaluated.

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; Monobactams; Nebuliser; Others anti-bacterial agents; Penicillins; Quinolones; Tetracyclines;