

Antibiotics for prevention of respiratory exacerbations

Inhaled antibiotics in cystic fibrosis

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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](#)).

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

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 fosfomicin-tobramycin.

A recent CDSR ([Smith S. 2018](#)) 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 inhaled anti-pseudomonal antibiotic treatment probably improves lung function and reduces exacerbation rate, but pooled estimates of the level of benefit were very limited. The best evidence 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 concludes 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.

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, efficacy 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 efficacy 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.

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. 2019](#)). 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 ALI was noninferior to cyclical twice-daily TIS in improving lung function.

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 2016, 41,2 % of the North American CF centers recommend inhaled aztreonam lysine in the population older than 6 years with chronic infection by *PA* ([2016 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.

Two studies were published after the last update of CDSR on inhaled antibiotics. The first ([Wainwright CE. 2011](#)) regarded CF patients with mild lung disease, where AZLI-treated patients preserved lung function and suppressed *PA* compared with placebo. The second ([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](#)).

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.

CIPROFLOXACIN DPI

Ciprofloxacin 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; $p=0.02$). Ciprofloxacin DPI showed positive effects on sputum bacterial load and quality of life, but these effects were not maintained at the 4-week follow-up. Ciprofloxacin DPI was well tolerated and there were no significant differences in type/incidence of treatment-emergent adverse events by treatment group ($p=0.115$).

COLISTIN

In 2016, a median of 9.1 % of the North American CF centers recommend inhaled colistin chronically in the population over 6 years of

age ([2016 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.

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*. 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, developed for the management of CF patients with chronic infections due to *PA*. One levofloxacin inhalation solution (LIS) was recently developed.

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 FEV₁ 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 ≥12 years with chronic *PA* infection. Time to exacerbation was the primary endpoint. FEV₁ (% 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 FEV₁ (% predicted mean difference 1.31%, p=0.01 [95% CI 0.27; 2.34%]) at 28 days was observed and LIS was well tolerated.

Finally, 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.

TOBRAMYCIN

In 2015, 70.2 % of the North American CF population older than 6 years with chronic infection by *PA* used inhaled tobramycin (2015 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.

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 recently 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](#)). However, this question may not be fully addressed until the ongoing prospective clinical trial testing this theory is completed (NCT02677701).

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 FEV₁ % 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-ethical 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?

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.

Some ongoing trials (2017):

Aztreonam Aerosol to Treat Cystic Fibrosis Nasal Disease - Phase 2 ([NCT02730793](#))

Combined Dry Powder Tobramycin and Nebulized Colistin Inhalation in CF Patients - Phase 3 ([NCT03341741](#))

Safety and Efficacy of 2 Treatment Regimens of Aztreonam for Inhalation Solution in Children With Cystic Fibrosis and New Onset *Pseudomonas Aeruginosa* Infection - Phase 3 ([NCT03219164](#))

Aztreonam Lysine: one HTA is ongoing

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-ethical 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 FEV₁ % 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;