Antibiotics for prevention of respiratory exacerbations

Inhaled antibiotics in cystic fibrosis

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Background

Inhaled antibiotics (iAB) in cystic fibrosis (CF) aim to reduce the bacterial load in the lung, thereby mitigating lung damage, slowing the decline in lung function, and decreasing the frequency of pulmonary exacerbations. are expected to translate into improved quality of life and survival.

Additional considerations related to inhaled antibiotic therapy in CF include financial cost, treatment burden, risk of drug-related adverse effects, and the potential for selecting antibiotic-resistant organisms with long-term exposure. A review of approved and emerging aerosolized antibiotics was published by Doring G et al., and an updated overview was later provided by Tai GTP et al.

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

Recently, the paranasal sinuses have been recognized as an important reservoir for colonizing bacteria in many people with CF. These sinuses often harbor distinct bacterial subpopulations, and during early colonization, migration from the sinuses to the lower airways appears to occur, suggesting independent adaptation and evolution in the sinus niche. Inhaled antibiotics could therefore play a role in preventing lower airway colonization.

An important issue is to evaluate how local airway conditions affect the clinical efficacy of aerosolized antibiotic after deposition in CF airways. Indeed, once deposited, the local activity of inhaled antibiotics may be reduced by interactions with molecules in CF mucus and the alginate matrix surrounding *Pseudomonas aeruginosa* (PA) (Bos AC, 2017).

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

Despite these recommendations, the use of inhaled antibiotics varies widely among countries. In The US, the 2019 CFF Patient Registry reported that among *P. aeruginosa*-positive patients aged ?6 years, 68.2% used inhaled tobramycin and 43.5% used inhaled aztreonam. In Europe, use ranged from 55% in the UK to 47% in Germany and 37% in Italy (European CF registry 2018). Naehrig S et al. (Naehrig S, 2023) analyzed data from the German CF Registry, describing inhaled antibiotic use among pwCF with intermittent or no *P. aeruginosa* infection. Among 1,960 pwCF with chronic *P. aeruginosa* infection, 90% (n = 1,751) received at least one inhaled antibiotic. The most frequently used agents were colistin (55.2%), aztreonam (32.6%), and tobramycin (30%). About 56% of adults and 44% of children alternated two inhaled antibiotics. It remains to be seen how the introduction of highly effective modulators such as elexacaftor/tezacaftor/ivacaftor (ETI) will affect inhaled antibiotic use.

The advent of CFTR modulators is expected to substantially alter CF airway microbiology. People with CF, their families, and caregivers often rank airway clearance techniques and inhaled antibiotics among the most burdensome therapies. In the coming years, the need for inhaled antibiotics may be re-evaluated (Elborn JS,2023) . However, the impact of improved CFTR activity on airway infections remains uncertain. The PROMISE-Micro Study Group reported that treatment with ETI produced large and rapid reductions in traditional CF pathogens in sputum, yet most participants remained infected with pre-existing organisms (Nichols D, 2023).

A recent review summarized current challenges related to antibiotic-resistant lung infections and discussed innovative inhaled formulations and delivery technologies designed to improve eradication of biofilm-associated bacteria (Islam N, 2024).

Another recent review explored the evolving approach to *P. aeruginosa* infection management, including detection, treatment burden, and the potential influence of CFTR modulators on the lung microbiome. The authors emphasized the need for updated guidance on diagnosis and management of *P. aeruginosa* infection and called for prospective studies to evaluate the effects of discontinuing inhaled antibiotic therapy in pwCF with chronic *P. aeruginosa* infection receiving CFTR modulators (Burgel PR, 2024). Two years after ETI initiation, reductions in the use of several routine therapies were documented in a national Danish CF cohort, with the largest decreases observed for airway medications and antibiotics, underscoring ETI's impact beyond traditional clinical metrics (Raket HK, 2024).

Analysis of data from the US CFF Registry examined pwCF with chronic, intermittent, or negative *P. aeruginosa* status, assessing demographic factors, predictors of inhaled antibiotic prescription, and trends from 2011 to 2019. The proportion of pwCF with chronic or intermittent *P. aeruginosa* infection decreased, while antibiotic prescription rates rose in these groups but declined in *P. aeruginosa* -negative individuals. Hispanic ethnicity, female sex, pancreatic insufficiency, CF-related diabetes, and ivacaftor/lumacaftor therapy were associated with higher antibiotic prescriptions across infection statuses. Among *P. aeruginosa*-negative pwCF, prescriptions were higher for those with *Burkholderia* spp. (OR 1.17, 95% CI 1.03–1.34) or MRSA (OR 1.45, 95% CI 1.26–1.68), but decreased over time. Prescriptions for Aspergillus increased (OR 1.6, 95% CI 1.3–1.8) in 2019. In pwCF on ivacaftor, antibiotic prescriptions decreased, becoming lower in 2019 for both chronic and *P. aeruginosa* -negative patients (OR 0.7, 95% CI 0.5–0.8). These findings indicate evolving treatment practices and health trends in pwCF even before the widespread introduction of triple modulators (Muhleback MS, 2025).

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 long-term use of inhaled antibiotics to suppress chronic infection in people with cystic fibrosis (CF) is widespread. The most commonly used drugs are tobramycin, colistin, aztreonam lysine, and, more recently, levofloxacin. Other agents currently in development include amikacin, ciprofloxacin, and the combined fosfomycin–tobramycin formulation.

A recent *Cochrane Database of Systematic Reviews* (CDSR) article (Smith S, 2022) evaluated the effects of long-term inhaled antibiotic therapy in CF on clinical outcomes (lung function, exacerbation frequency, and nutritional status), quality of life and adverse events (including hypersensitivity reactions and survival). The authors concluded that prolonged treatment with inhaled anti-pseudomonal antibiotics likely improves lung function and reduces exacerbation rates, although pooled estimates of the magnitude of benefit were limited. The strongest evidence supports the use of inhaled tobramycin. Additional trials using standardized outcome measures are needed to better define treatment benefit. Longer studies are also required to assess the effects of inhaled antibiotics on quality of life, survival, and nutritional outcomes.

Another CDSR assessed the effectiveness, safety, treatment burden, and adherence associated with various nebulizer devices (Daniels T, 2013). The review concluded that clinicians should be aware of performance variability among nebulizer systems. Technologies such as adaptive aerosol delivery and vibrating mesh nebulizers offer advantages over conventional systems in terms of treatment time, drug deposition efficiency, patient preference, and adherence. Long-term randomized controlled trials (RCTs) are required to evaluate patient-centered outcomes (such as quality of life and treatment burden), optimal dosing, clinical endpoints (hospitalizations, antibiotic use), and cost-effectiveness.

Several reviews from the Database of Abstracts of Reviews of Effects (DARE) have also addressed this topic. A review by Littlewood KJ, 2012 compared the efficacy of inhaled tobramycin (solution and powder), colistimethate sodium (solution) and aztreonam lysine for inhalation (AZLI) using data from RCTs. The authors conclude that all examined antibiotics showed comparable efficacy in the management of chronic PA lung infection in CF.

Another systematic review (Maiz L, 2013) analyzed the three available inhaled antibiotics (aztreonam lysine (AZLI), colistin (COL) and tobramycin (TOB). The authors concluded that treatment choice should be individualized based on drug characteristics (clinical efficacy and safety), the delivery system, and patient factors.

A further DARE review (Tappenden P, 2013) evaluated the clinical and cost-effectiveness of colistimethate sodium dry powder for inhalation (DPI) (Colobreathe(®), Forest Laboratories) and tobramycin DPI (TOBI Podhaler(®), Novartis Pharmaceuticals) for treating P. aeruginosa lung infection in CF. Both DPI formulations were found to be non-inferior to nebulised tobramycin in terms of FEV1% predicted. However, the authors noted the need for high-quality studies to clarify the relationship between lung function measures (such as FEV?%) and survival or health-related quality of life (HRQoL).

Long-term inhaled antibiotictherapy is recommended for people with cystic fibrosis (pwCF) chronically infected with Pseudomonas aeruginosa (PA). Nonetheless, inhaled antibiotics are also commonly prescribed to pwCF without chronic PA infection. A registry-based study from the EU CF registry examined the prevalence and determinants of inhaled antibiotic use in pwCF without chronic PA infection, and assessed associated long-term outcomes. Treatment was more common in individuals with severe genotypes, diabetes, pancreatic insufficiency, or a history of chronic PA infection (OR 3.8, 95% CI 2.88–5.04). Inhaled antibiotic use was not associated with reduced acquisition of PA or other resistant pathogens, nor with improved lung function decline, survival, or transplantation outcomes. These findings underscore the need for controlled studies evaluating pathogen-specific and indication-specific inhaled antibiotic regimens. (Orenti A, 2022).

Inhaled antibiotics may also increase the risk of treatment-emergent respiratory organisms. A study from the Canadian CF registry found that inhaled antibiotic use was associated with increased acquisition of *A. fumigatus* among PwCF with intermittent Pa infection (HR 1.43, 95 %CI; 1.08–1.88; p = 0.01) and among Pa negative individuals (HR 2.44, 95 %CI; 1.65–3.61; p < 0.001), but not among those with chronic Pa infection (HR 1.36, 95 %CI; 0.94–1.95; p = 0.10). No associations were found between inhaled antibiotic use and acquisition of S. maltophilia or Achromobacter spp. (Cogen JD, 2025)

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.* Overall, AZLI appears to have an acceptable tolerability and safety profile in children and adolescents, though careful monitoring is warranted, especially for severe respiratory events (Valmir N, 2025).

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

More consistent results are needed regarding lung function outcomes and definitions of respiratory exacerbations in terms of hospitalization and antibiotic use. The effects of long-term inhaled antibiotic therapy on quality of life and survival also require evaluation. The magnitude of clinical benefit remains uncertain, as most trials are small and short in duration; thus, evidence of long-term benefit is lacking. Optimal dose regimens for several antibiotics are not yet established, nor is the best method of aerosol generation and delivery. Treatment-related harm may be underestimated in short-term RCTs, particularly regarding the emergence of antibiotic-resistant pathogens during prolonged use.

Specific issues that warrant further investigation include:

1. Comparing colistin (including different dosing regimens) to other antibiotics for efficacy and safety, since placebo-controlled trials are now considered unethical.
2. Determining the optimal dose, daily frequency, and duration of inhaled antibiotic therapy. While treatment was initially approved for intermittent administration, continuous alternating regimens involving different antibiotic combinations should be evaluated for potential added clinical benefit.
3. Conducting longer-term comparative studies of tobramycin and colistin, including combination or continuous alternating therapy approaches.
4. Assessing the adverse effects of long-term inhaled antibiotic use, particularly regarding the development and clinical impact of antibiotic-resistant organisms.
5. Investigating new drugs or formulations, and evaluating their role in early eradication regimens for CF patients at first identification of *Pseudomonas aeruginosa* (PA) infection.

6. Addressing the following clinical questions related to pulmonary exacerbations in CF:
    - For mild exacerbations, does the addition of an inhaled antibiotic to oral therapy improve outcomes compared to oral therapy alone?
    - For more severe exacerbations, is an inhaled antibiotic as effective as its intravenous formulation when added to other IV antibiotics?
7. Evaluating whether long-term inhaled anti-PA therapy should be discontinued in children who achieve sustained PA negativity. Many children initiated on chronic inhaled anti-PA therapy subsequently produce PA-negative samples for extended periods. Determining whether PA has been eradicated or merely suppressed requires treatment discontinuation and subsequent culture monitoring.
8. Understanding how the introduction of the highly effective modulator elexacaftor/tezacaftor/ivacaftor (ETI) will influence the use of inhaled antibiotics (Elborn JS, 2023).
9. Prescriptions of inhaled antibiotics for non-chronic Pa

Regarding issue 2, a double-blind trial compared continuous alternating therapy (CAT) with intermittent treatment (Flume PA, 2016). Participants received three cycles of 28 days of inhaled aztreonam (AZLI) or placebo, each alternating with 28 days of open-label tobramycin inhalation solution (TIS). The trial indicated that AZLI/TIS CAT was well tolerated and might provide additional clinical benefit compared with intermittent TIS alone. AZLI/TIS reduced exacerbation rates by 25.7% (p = 0.25) and hospitalization rates by 35.8% (p = 0.14) compared with placebo/TIS. Although trends favored CAT, results were not statistically significant, likely due to insufficient sample size. Further studies are warranted.

Regarding issue 6, an open-label randomized crossover study evaluated the substitution of inhaled aztreonam lysine (AZLI) for an intravenous antibiotic in the management of acute pulmonary exacerbations (Frost F, 2021). In adults with CF and *P. aeruginosa* infection, AZLI plus IV antibiotics improved lung function and quality of life compared with IV antibiotics alone. These findings support larger trials to define the role of inhaled antibiotics in acute exacerbations. (Frost F, 2021).

A recent CDSR review examined whether inhaled antibiotics improve quality of life, reduce time off school or work, and enhance long-term lung function when used for pulmonary exacerbations in CF (Smith S, 2022). The authors identified only low- or very low-certainty evidence due to small, underpowered trials. No clear superiority of any treatment was demonstrated. Further research is needed to determine whether inhaled tobramycin can serve as an alternative to intravenous tobramycin for some exacerbations. To date, inhaled antibiotics have not been adequately studied as standalone therapy in acute exacerbations.

A real-world pilot study from Israel investigated dual inhaled antibiotic therapy as an alternative to IV antibiotics for pulmonary exacerbations. Patients with signs of exacerbation unresponsive to oral antibiotics but judged not to require IV therapy received dual inhaled antibiotics. Among ten treated patients, eight reported clinical improvement (mainly reduced cough, sputum, and dyspnea), all reported full adherence, and no adverse effects occurred. The findings suggest that dual inhaled antibiotics may promote recovery in mild exacerbations and could be considered before initiating IV therapy. Randomized controlled trials are required to define when this approach is appropriate (Heching M, 2024).

Regarding issue 7, a UK registry-based study and accompanying survey examined practices across 29 pediatric CF centers regarding cessation of anti-PA therapy in children who became PA-negative (Gilchrist FJ, 2023). Responses were received from 23 centers (79%), of which 22 (96%) discontinued anti-PA nebulized therapy once PA clearance was achieved. Most centers defined discontinuation after one to two years of negative cultures, though durations ranged from three months to three years. Criteria varied, including sampling frequency, clinical stability, PA phenotype, and physiotherapy adherence. Although many centers stop anti-PA therapy after sustained clearance, no standardized approach exists and re-isolation rates remain unknown. Controlled trials are urgently needed to determine safe discontinuation intervals. Stopping unnecessary inhaled antibiotics could reduce costs, treatment burden, side effects, and antibiotic resistance. (Gilchrist FJ, 2023).

Regarding issue 9, an ECFS-based registry study showed that actors associated with iAB regardless of Pa were pancreatic insufficiency, azithromycin and mucolytics. Markers of worse disease and S. maltophilia positive cultures were associated with iAB for pwCF without chronic Pa. Over time, chronic Burkholderia infection was associated with increasing odds of iAB. (Muhleback MS, 2025)

Tobramycin versus colistin: unresolved questions

- Comparative studies of colistin (at different doses) versus other antibiotics are needed, as placebo comparisons are now unethical.
- Long-term head-to-head or combination studies of tobramycin and colistin, including continuous alternating regimens, should be conducted.

Tobramycin: ongoing research questions

- Determination of optimal dosing schedule, mode, and frequency of administration.
- Long-term comparative studies with colistin and evaluation of combination regimens.
- Characterization of long-term adverse effects, especially the emergence of resistant organisms.
- Exploration of tobramycin nasal solution (TNS) as a potential alternative to IV aminoglycosides during pulmonary exacerbations. In a randomized crossover pilot trial, Al Aloul M et al, compared 14 days of IV tobramycin versus TNS in 20 adults with CF and chronic PA infection, both receiving IV colistin. Improvements in spirometry were similar between groups [mean FEV? % predicted: IV 16.4 (SD 8.5) vs. TNS 19.9 (SD 11.3); p = 0.26], but sputum PA suppression was greater with TNS. IV tobramycin caused higher urinary protein excretion and markers of tubular injury. Further studies are warranted to validate these findings.

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;