Aerosolized Antibiotics for Non-Cystic Fibrosis Bronchiectasis

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\textbf{Introduction}

Bronchiectasis is a pathological condition whereby the walls of the airways become progressively weakened due to repeated injury and obstruction. Damage is cumulative and results in abnormally dilated and thickened bronchial walls. Clinical manifestations vary from patients being asymptomatic to experiencing symptoms daily. The most common symptoms are nonspecific and include cough, sputum expectoration and lethargy, while more severe manifestations include hemoptysis, chest pain, shortness of breath and decreased exercise tolerance\cite{1}.

The conditions associated with the development of bronchiectasis are broadly categorized as postinfectious damage, abnormal host defenses, genetic defects, congenital malformations, mechanical obstruction, chronic inflammatory conditions and autoimmune disease. In at least half the cases, however, a cause cannot be determined\cite{2–5}.

The vicious cycle hypothesis posits that inflammation predisposes to chronic infection (called chronic suppurative lung disease) with the host response contributing to airway damage, which then sustains the inflammation\cite{1, 6}.

Though not the most common cause of bronchiectasis, cystic fibrosis (CF) is perhaps the best-studied. The pathogenesis of bronchiectasis in CF stems from a genetic abnormality that predisposes to chronic lung infection and a persistent inflammatory state within the lung. The progression of lung damage and the development of bronchiectasis in CF closely match the vicious cycle hypothesis; this is used as a starting point for therapy in non-CF bronchiectasis (NCFB) [7].

Problems Arise because NCFB Is Not CF

Despite having common symptoms, therapies effective for the treatment of CF have not always been beneficial in treating NCFB [7]. The use of nebulized dornase alfa has not only been unhelpful, but even harmful and associated with increased frequency of exacerbations and an accelerated decline in lung function [8–10]. Another mainstay of therapy for CF lung disease is tobramycin solution for inhalation, but results have been disappointing when using it for NCFB [7], with study patients more likely to report cough, dyspnea, wheezing and chest pain than those on a placebo. There was also no improvement in measured lung function [11].

The great heterogeneity among the conditions called NCFB may be impeding the development of effective therapies. No animal model has been found to be adequate, so basic scientific research is limited [7]. Furthermore, populations of patients are often too small for clinical investigations to produce generalizable results [12]. Interpretation of results can also be difficult because there is no standard approach to diagnosing an exacerbation of NCFB lung disease as there is in CF [13, 14]. Correlations between low FEV₁, dyspnea and increased mortality have been reported [13]. Factors contributing to/associated with these include increased cough and sputum expectoration, wheezing, declining exercise tolerance, chest X-ray changes and pathological chest sounds, with some or all of these often being used to qualify an exacerbation [15–17]. Studies on children have reached similar conclusions, with an exacerbation being closely correlated with a wet cough and worsening cough severity, while spirometry may be less helpful [18].

Approach to Treatment

Currently, no medications have been approved for the treatment of NCFB in the USA [7], but from a practical standpoint, treatment must still be provided. Following the vicious cycle hypothesis, inflammation is a key contributor to the development and progression of NCFB. Antibiotics are routinely employed in treatment due to the increasing evidence supporting the role of bacteria in promoting and continuing inflammation [19, 20] and likely a direct correlation between bacterial load and both airway and systemic inflammation [6, 13, 21, 22] (even though this does not always correlate with clinical outcomes [7, 23]).

An understanding of the microbial milieu in CF lung disease has grown over decades and continues to evolve, and it seems that similar organisms are associated with NCFB [10]. NCFB patients frequently harbor Pseudomonas aeruginosa, Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus and Moraxella catarrhalis [14, 22, 24], and although Aspergillus and nontubercular Mycobacterium have not been investigated as thoroughly, the evidence available suggests that these are sometimes discovered in NCFB [3, 22, 25]. An exception may be the Lady Windermere syndrome, though this is increasingly associated with CFTR gene mutations [26, 27]. The role of individual bacteria in the pathogenesis of NCFB has not been clearly established. P. aeruginosa is found in approximately 25% of patients with NCFB [28], and it has been associated with more frequent exacerbations, faster disease progression and increased mortality [20, 22, 24, 29, 30].

The number of clinical trials investigating antibiotic therapy in NCFB is small [12, 23]. Azithromycin and other macrolides are some of the more thoroughly investigated drugs for NCFB [12], and evidence is accumulating that such treatment can improve both microbiological and clinical outcomes [12, 31]. Investigations into both long- and short-term use of other systemic antibiotics have produced conflicting results; they suggest that treatment does reduce bacterial load but they do not conclusively show significant clinical benefit [32–34]. Advances in aerosol delivery in recent years have shifted the focus of research to inhaled antibiotic therapy for NCFB, but the early results are conflicting, showing less benefit than expected compared to the results in CF patients [33].

Aerosols Delivering High Concentrations of Antibiotics

The advantages of inhaled medication delivery have been well described. Irrespective of the medical condition, a key limitation for its use has been the difficulty of safely achieving therapeutic drug levels within the lung.
Improvements in nebulizer technology have greatly increased delivery efficiency, which is approximately 10% of the loading dose with conventional nebulizers [35]. Newer systems like eFlow® (PARI Pharma GmbH, Munich, Germany), I-neb AAD (Adaptive Aerosol Delivery; Philips Respirationics, Chichester, UK) and AKITA® APIXNEB™ and FOX™ (Vectura, Chippenham, UK) are able to achieve >70% delivery efficiency in some settings [36].

There are continuing improvements in drug design, with the emergence of aerosolized formulations that are well tolerated at the epithelial surface, able to penetrate infected sputum and capable of evading immune system clearance long enough to achieve a therapeutic response [33]. The antibiotics chosen for study are often those with concentration-dependent effects, i.e. a greater AUC/MIC ratio improves killing, as it is possible to achieve very high concentrations of the drug in the airway without the corresponding systemic side effects; this is advantageous for overcoming bacterial resistance [14, 34, 37].

**Antibiotics under Investigation for Aerosol Delivery in NCFB**

Novel formulations and aerosolized antibiotic formulations already approved for use in CF are being investigated specifically for use in NCFB.

### Tobramycin

Tobramycin is widely used for inhalation therapy to treat CF lung disease. It is currently available in a liquid form for nebulization and as a dry powder for inhalation. It is also the most-studied inhaled antibiotic for use in NCFB. Results in patients infected with *P. aeruginosa* have generally been consistent. In NCFB, inhaled tobramycin, with or without other antibiotics, reduces bacterial density on culture but fails to improve lung function or quality of life measurements [11, 38–40]. One open-label and uncontrolled study that followed only symptom and quality of life scores reported an improvement after three cycles of therapy [41]. All the studies have reported that inhaled tobramycin is frequently not tolerated well in this patient population [10, 20].

### Aztreonam

Inhaled aztreonam is currently approved for use in CF lung disease. To date, there has been little investigation into its use in NCFB. The results of the AIR-BX1 and AIR-BX2 trials were presented in 2013, but these did not show any clinical benefit based on symptom scores and time to exacerbation [42].

### Colistin

Nebulized colistin has primarily been studied in the context of CF lung disease, but has also been investigated for use with ventilator-associated pneumonia and, in a limited capacity, for NCFB. Though it is generally well-tolerated, no study has been able to deliver significantly impressive results. There is also no agreement on the optimal dose, as the pharmacokinetic and pharmacodynamic properties of the inhaled form have not been determined. As such, inhaled colistin has not gained FDA approval, and its use remains off-label [43].

Investigations targeting NCFB have mostly reported improvements in quality of life, although in one study, these data were collected retrospectively [44] and in another, this was a secondary end point [20]. One study reported that colistin use slowed the decline of FEV₁ [44], but others found no change [20, 45]. Each study reported longer times to exacerbation while using colistin [20, 44, 45].

### Gentamicin

There has been limited investigation into the use of nebulized gentamicin in NCFB, but early results were favorable. A year-long study showed that its use led to significant reductions in sputum bacterial density and markers of airway inflammation and improvements in exercise tolerance and patient-reported quality of life [46].

### Ciprofloxacin

With promising early results and the availability of different formulations, ciprofloxacin appears to be the most actively investigated drug for use in NCFB. The ORBIT (Once-Daily Respiratory Bronchiectasis Inhalation Treatment) studies are investigating liposomal ciprofloxacin for inhalation. Two formulations are under investigation: ARD-3100 (Lipoquin™, Aradigm Corp., Hayward, Calif., USA) is a liposomal formulation and ARD-3150 (Pulmaquin™, Aradigm Corp.) is a dual-release mixture of ARD-3100 with unencapsulated ciprofloxacin.

ORB1T-1, a phase IIB study, showed that Lipoquin use resulted in a significant decrease in *P. aeruginosa* growth from sputum culture, and that the medicine was very well tolerated [47]. Another phase IIB study, ORBIT-2, showed similar efficacy and tolerability with Pulmaquin and a greater time to exacerbation [17]. ORBIT-3 and ORBIT-4, both phase III studies, will investigate the time...
to first pulmonary exacerbation, safety and efficacy in NCFB patients chronically infected with *P. aeruginosa* [48, 49].

Bayer has developed ciprofloxacin for dry powder inhalation (DPI) using PulmoSphere™ technology (Novartis) that is also being investigated for use in NCFB. Results for a phase II study show that twice-daily use for 28 days yields a statistically significant reduction in bacterial load [50]. As opposed to the ORBIT studies which limited their surveillance to *P. aeruginosa*, this study tracked all organisms and demonstrated efficacy against mucoid *P. aeruginosa*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (fig. 1). Two phase III studies, RESPIRE 1 and RESPIRE 2, are ongoing and will continue to investigate clinical efficacy and safety of ciprofloxacin DPI [51, 52]. In April 2014, this formulation was granted orphan drug designation for use in NCFB by the Food and Drug Administration in the USA [53].

*Levofloxacin*

Pulmatrix Inc. (Lexington, Mass., USA) is developing a dry powder formulation of levofloxacin (PUR0400) using novel iSPERSE™ (inhaled small particles easily respirable and emittable) technology. Its use is envisioned for CF and NCFB, but it is still in preclinical development [54]. Updated information on its physical and aerosol properties and the stability of the product was presented at the 2014 Respiratory Drug Delivery Conference.

*Amikacin*

Liposomal formulations of amikacin have been investigated for the treatment of *P. aeruginosa* infection in CF and nontubercular *Mycobacterium* with promising early results. A phase III study for use in NCFB is ongoing [55].

*Antibiotic Enhancers*

There is great interest in adjuncts that improve antibiotic activity, increase retention within the lung and reduce cytotoxicity. Many are in preclinical investigations for use in CF, and are being viewed as likely candidates for treating NCFB.

Certain metals are known to have antimicrobial properties and have shown promise in the treatment of lung infection, especially by *P. aeruginosa*. Studies in vitro have shown that bismuth interferes with biofilm production [56] and that, when encapsulated with tobramycin within...
a liposome, can increase antibiotic efficacy against common respiratory pathogens [57]. This formulation is able to penetrate CF sputum [58] and has shown antibiotic effectiveness at lower concentrations with improved targeting [59]. In addition to biofilm effects, there is also an interruption of quorum sensing, signaling molecule production and a decreased secretion of virulence factors [60].

In vitro investigations with gallium using CF sputum have identified a disruption of iron metabolism that prevents biofilm production and retards the growth of P. aeruginosa [61]. A liposomal formulation of gallium and gentamicin has also shown greater antibiotic efficacy than the use of gentamicin alone against P. aeruginosa growing in a biofilm in CF sputum [62].

Liposomal formulations are attractive in NCFB because they can be effectively aerosolized. They also offer the advantage of reducing the cytotoxicity of the encapsulated products by improving delivery, which allows reduced dosing [58, 62, 63]. Dosing reduction is also facilitated by surface modification of the lysosomes, i.e. PEGylation, which helps avoid immune system recognition and delays clearance [64].

Combination antibiotic therapy is also an area of active investigation, possessing the advantages of a broadened spectrum of activity, an improved efficiency of administration and synergistic antimicrobial effects which allow for reduced dosing. A combination of fosfomycin and tobramycin has shown efficacy in vitro against respiratory pathogens common in CF and NCFB [65, 66] and has been administered as an aerosol to adults with CF in early clinical trials [67]. This combination has also demonstrated synergistic bactericidal effects and eradicated P. aeruginosa biofilms in vitro [68]. Aerosol delivery of a combination of amikacin and fosfomycin has been shown to achieve adequate drug concentrations in intubated patients with ventilator-associated pneumonia without adverse effects, although the clinical response here was not actually reported [69]. There has also been a demonstration of synergy with a combination of colistin and tobramycin in vitro, in a rat model and in an early clinical trial with CF patients [70].

### Emergence of Bacterial Resistance

With aerosol delivery, antibiotic concentrations in the proximal airway can greatly exceed those obtained safely by other means [71]. There is an advantage to delivering antibiotics that have greater efficacy at higher AUC/MIC ratios, as this can help to overcome efflux pump-driven bacterial resistance [33, 71]. Unfortunately, aerosol delivery to the lung is not uniform, and this has the potential to create antibiotic concentration gradients, i.e. much lower concentrations are found in deeper parts of the lung [33]. Continued subtherapeutic exposure allows bacterial adaptation and fosters the development of resistance [72].

It is now recognized that most of the bacteria associated with chronic infection in CF, NCFB and other conditions are capable of biofilm formation. In addition to providing barrier protection against antibiotics, this also establishes a sustained, protected environment that allows for lateral gene exchange and increases the likelihood of organisms acquiring more resistance [73].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study type</th>
<th>Population</th>
<th>N (n)*</th>
<th>Resistance</th>
<th>Duration</th>
<th>Reference, first author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin</td>
<td>prospective</td>
<td>NCFB and COPD</td>
<td>18 (18)</td>
<td>none</td>
<td>once daily for an average of 41 months</td>
<td>[44] Steinfort, 2007</td>
</tr>
<tr>
<td>Colistin</td>
<td>R, PC</td>
<td>NCFB with PA</td>
<td>144 (73)</td>
<td>none</td>
<td>twice daily for up to 6 months</td>
<td>[20] Haworth, 2014</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>DB, PC, crossover</td>
<td>NCFB with PA</td>
<td>20 (20)</td>
<td>10% b (to drug, to placebo)</td>
<td>twice daily for 6 months</td>
<td>[39] Drobnic, 2004</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>OL</td>
<td>NCFB with PA</td>
<td>31 (31)</td>
<td>6%</td>
<td>twice daily 14 days on/off for 12 weeks</td>
<td>[41] Scheinberg, 2005</td>
</tr>
<tr>
<td>Ciprofloxacin (DRCFI)</td>
<td>phase II DB, R, PC</td>
<td>NCFB with PA</td>
<td>37 (18)</td>
<td>none</td>
<td>once daily 28 days on/off for 24 weeks</td>
<td>[17] Serisier, 2013</td>
</tr>
<tr>
<td>Ciprofloxacin (DPI)</td>
<td>phase II DB, R, PC</td>
<td>NCFB with positive culture</td>
<td>124 (60)</td>
<td>10% b</td>
<td>twice daily for 28 days</td>
<td>[50] Wilson, 2013</td>
</tr>
</tbody>
</table>

DB = Double-blind; DRCFI = dual-release ciprofloxacin for inhalation; OL = open-label; PA = P. aeruginosa; PC = placebo-controlled; R = randomized.

* Number of patients who completed the study (number on the drug).

b Resistance lost after stopping therapy.
There is a growing understanding of the microenvironment within the CF lung, and particularly its role in the development of antibiotic resistance. In CF treatment, there have been limited reports of acquired resistance to tobramycin [74], but this is usually sustained for only a few months after stopping therapy [34]. There have also been reports of acquired resistance to aztreonam when used twice daily, but not when used 3 times a day [75]. Acquired resistance to colistin is rare [76].

While investigations to date have not identified a clinically relevant resistance to inhaled antibiotics in CF [77], concerns remain that continued and more widespread use will increase the risk of developing resistance [10]. There are known differences in antibiotic activity between the CF and non-CF lung, particularly with aminoglycosides and fluoroquinolones [71, 78], and this may change adaptation pressure. Outcomes in NCFB, however, appear similar to those in CF, including a likely loss of resistance after stopping therapy [50]. Our results are summarized in Table 1.

### Table 2. Active clinical trials, as of June 2014, studying aerosolized antibiotics for use in NCFB

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Identifier</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmaquin in NCFB (ORBIT-4)</td>
<td>III</td>
<td>NCT02104245</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>Dual-release ciprofloxacin for inhalation in NCFB (ORBIT-3)</td>
<td>III</td>
<td>NCT01515007</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Ciprofloxacin DPI in NCFB (RESPIRE 1)</td>
<td>III</td>
<td>NCT01764841</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Ciprofloxacin DPI in NCFB (RESPIRE 2)</td>
<td>III</td>
<td>NCT02106832</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Combined administration of nebulized amikacin in patients with acute</td>
<td>III</td>
<td>NCT02081963</td>
<td>Ongoing but not recruiting</td>
</tr>
<tr>
<td>exacerbation of NCFB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy and tolerability of the tobramycin podhaler in bronchiectasis</td>
<td>N/S</td>
<td>NCT02102152</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>patients with chronic <em>P. aeruginosa</em> infection (TOBI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic evaluation and tolerability of dry powder tobramycin</td>
<td>I, II</td>
<td>NCT02035488</td>
<td>Recruiting</td>
</tr>
<tr>
<td>by a novel device in patients with NCFB</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: ClinicalTrials.gov. N/S = Not specified.

### Discussion

Increasing recognition of the prevalence and burden of NCFB has spurred research into its epidemiology, pathogenesis and management. It is clear, despite the variety of causes, that NCFB is sufficiently distinct in many ways from CF, and that a default approach of using therapies proven in CF is not adequate and is even potentially counterproductive. Antibiotic therapy for acute and chronic infections has shown variable results. Treatment clearly reduces bacterial load as well as symptoms like cough and sputum expectoration to the point that improvements in the quality of life of patients have been demonstrated.

Preferred antibiotics and routes of delivery for management have not been established. There is growing interest in pursuing aerosol delivery because of its convenience and lower side-effect profiles, although admittedly, this has been biased due to the demonstrated successes with CF. Technological advancements in aerosolization and drug development have enabled investigation of novel therapies and the initial results are promising, with different formulations of ciprofloxacin and amikacin entering phase III trials. Alternative formulations of inhaled tobramycin, which may prove to be better-tolerated, are at the stage of early clinical trials (Table 2). It is too early to speculate on the efficacy and cost benefits of therapy.

### References
