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Duration of antibiotic therapy in non-cystic fibrosis bronchiectasis

R. Somayaji¹, C.H. Goss^{2,3}

¹Departments of Medicine and Microbiology, Immunology & Infectious Disease, University of Calgary, Calgary, Alberta CA

²Departments of Medicine and Pediatrics, University of Washington School of Medicine, Seattle WA

³CFF Therapeutics Development Network Coordinating Center, Seattle Children's Research Institute, Seattle WA

Abstract

- a) Purpose of review:** We conducted a review of the current evidence relating to antibiotic duration in the short and long-term management of non-cystic fibrosis bronchiectasis.
- b) Recent findings:** In non-cystic fibrosis pulmonary exacerbations, evidence is primarily based on expert consensus and recent guidelines recommend antibiotic durations of approximately 14 days. Chronic antibiotics (oral or inhaled) are recommended in patients with frequent exacerbations or with chronic *Pseudomonas aeruginosa* airways infection. Macrolides are the best studied therapies for long-term use with evidence for effect limited to a 12 month duration. Encouragingly, there are increased efforts to develop registries and conduct larger population level studies to improve patient care.
- c) Summary:** There is a paucity of evidence for optimal antibiotic strategies in exacerbations and chronic maintenance in persons with non-cystic fibrosis bronchiectasis. Rationally designed studies which utilize a registry and population-based approach will be critical to build evidence-based strategies to optimize management of non-cystic fibrosis bronchiectasis.

Keywords

pulmonary exacerbation; non-cystic fibrosis bronchiectasis; treatment duration; FEV₁; respiratory symptoms

Introduction

Non-cystic fibrosis related bronchiectasis (nCFB) is a chronic pulmonary disorder without a cure. The course of nCFB is punctuated by acute exacerbations which can occur frequently and lead to further progression of lung disease and affect morbidity, mortality, and health care costs^{1–6}. There is a dearth of evidence and therapies for optimal management strategies

Corresponding author: Christopher Goss, MD MSc, 1959 NE Pacific St, Seattle WA 98195, Ph: (206) 598-4615, goss@uw.edu.

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specific to nCFB and exacerbations although national and international published guidelines are increasingly recognizing this need⁶. Herein we will review the current evidence relating use of short- and long-term antimicrobial therapies with a focus on exacerbations.

Evolution of nCFB

Non-cystic fibrosis related bronchiectasis (nCFB) is defined as bronchiectasis that is not due to cystic fibrosis (CF). The clinical manifestations of the disease focus on irreversible dilatation of bronchi with destruction of elastic and muscular components of their walls. While bronchiectasis can be identified on a chest radiograph, the gold standard method for diagnosis is via high resolution computerized tomography (HRCT) scan. The etiology of nCFB is often idiopathic in nature but may be a result of prior lung infections (i.e. tuberculous mycobacterial infection), anatomic obstruction, inflammatory diseases (i.e., rheumatoid arthritis, inflammatory bowel disease, allergic bronchopulmonary pulmonary aspergillus) and inherited disorders (i.e. primary ciliary dyskinesia, IgG subclass deficiency). The pathophysiology of the evolution of nCFB is thus multifactorial but involves abnormalities in airway structure and airway host immunity leading to chronic lower airway infection. This in turns leads to a cycle of chronic infection, inflammation and further airway damage⁷. A similar hypothesis has been proposed for the progressive evolution of bronchiectasis due to CF, although a larger body of evidence including *in vitro* and *in vivo* animal models evidence delineating the potential early steps leading to mucous obstruction and chronic lower airway infection^{8,9}.

Given how central chronic lower airway bacterial infection is in nCFB, it is important to know the specific pathogens that each patient harbors in their lower airway. The pathogens most frequently associated with nCFB are: *Haemophilus influenzae* (30-47%), *Streptococcus pneumoniae* (7-11%), *Pseudomonas aeruginosa* (12-31%), *Staphylococcus aureus* (4-7%), and *Moraxella catarrhalis* (2-20%)¹⁰. Using techniques to evaluate bacterial 16S rDNA pyrosequencing much as been done in CF, a number of groups have identified additional difficult to culture bacteria that may have relevance to treatment such as the anaerobic bacteria *Prevotella* and *Veillonella* species¹¹. Although it is possible that certain microbial species may be predictive of exacerbations (i.e. *Veillonella* species¹²), no evidence for addition of anaerobic-active antimicrobials exist, and other studies of exacerbations have demonstrated microbial community stability following treatment¹¹. Much as in CF, some of the best data to date regarding the clinical implications of specific lower airway infections related to *Pseudomonas aeruginosa*. Several studies have found associations of lower airway infection with *Pseudomonas aeruginosa* and subsequent pulmonary exacerbations and hospitalizations¹³⁻¹⁵. A more recent publication followed a cohort of 39 patients with nCFB based on biobanked specimens from 1986 to 2011 found distinct patterns of infection with 69% having a persistent single strain of *Pseudomonas aeruginosa* and 20% having strain displacement¹⁶. Differential patterns of infection were not associated with worsened clinical outcomes in this study although a greater frequency of strain displacement occurred in contrast to persons with CF¹⁶. Of note, in the limited literature available, cross-infection with *Pseudomonas aeruginosa* in nCFB seems to be a rare event¹⁷.

As in other chronic lung diseases like CF and chronic obstructive pulmonary disease (COPD), patients often experience episodes of worsening lung pulmonary symptoms with increased sputum volume, sputum viscosity, and cough frequency. They can also experience wheeze, chest tightness, pleurisy and hemoptysis. These events have been termed “exacerbations” and may be due to superimposed viral infections with subsequent clonal expansion of existing organisms or acquisition of new bacterial pathogens in the lower airway. The recent consensus statement defined these events as follows¹⁸: “a deterioration in three or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; hemoptysis AND a clinician determines that a change in bronchiectasis treatment is required.” This definition in many ways mirror the current definition of a pulmonary exacerbation used in CF clinical trials. Much like CF, these events are integral in the natural history of the disease.

Wilson et al (2013) have published about other potentially pathogenic microorganisms (PPMs) such as *Klebsiella* spp (7%) and *Proteus* spp (6%). However, the link between colonization by a specific bacteria and exacerbation is often difficult to demonstrate. Several studies tried to identify the predictors of morbidity in non-CFB exacerbations. Among them colonization with *P. aeruginosa* may play a key role^{13–15}. Non-CFB exacerbation prevalence is not well defined; in a US cohort using a claims database (with the cohort definition having a combination of diagnostic criteria) estimates range from 4.2 cases per 100,000 persons aged 18–34 years up to 272 cases per 100,000 in those over 75 years with an overall mean age of 61 years¹⁹. Most subjects (68%) were women and common comorbidities included COPD (30.1%), ischemic heart disease (12.6%), malignant neoplasms (11.4%), diabetes mellitus (8.9%), and heart failure (8.1%).

Overview of antimicrobial therapies

Despite the economic burden of nCFB, there are no therapies that have been specifically licensed by major regulatory bodies for its management⁶. Therapeutic decisions and algorithms have to date largely been derived from CF though their heterogeneity in pathophysiology, disease evolution, and clinical response demonstrates the need for dedicated studies^{20,21}. The classes of therapies used in nCFB broadly fall into the following categories: bronchodilators, mucolytics, anti-inflammatories and antimicrobials.

Antimicrobial therapies are short-term for purposes of eradication and management of pulmonary exacerbation, or for chronic maintenance of lung health in nCFB. Oral, inhaled, or intravenous antibiotics may be used in isolation or combination based on the patient, setting, and provider preferences. Eradication refers to treatment with the intent to clear the airways of a pathogen and is only recommended for new airways infection with *Pseudomonas aeruginosa* based on expert consensus^{22–24}. The remainder of this review will focus use of therapies on management of pulmonary exacerbations and chronic maintenance of pulmonary health.

Treatment considerations for pulmonary exacerbations

Exacerbations in nCFB are associated with airways inflammation and lung damage^{1,2,25}, and have an impact on morbidity³, mortality², quality of life⁵, and health care costs⁶. Recent data from the EMBARC Bronchiectasis Registry has demonstrated that ~50% of patients had two or more exacerbations annually and one in three required hospitalization²⁶. Expectedly, much of the focus is on therapies to prevent or reduce exacerbation occurrence. Exacerbation treatment in nCFB is typically based on knowledge of the patient's airway microbiology, severity, and clinical response, and may be further influenced by patient, provider, and health system aspects.

In regards to treatment duration for an exacerbation, the expert consensus in recent guidelines suggests 14 days and is consistent with prior guideline iterations^{6,27–29}. A Delphi study published in 2014 reached consensus for use of 10 to 14 days for nCFB exacerbation and use of combination antibiotics only with history of *P. aeruginosa* infection³⁰. There is very little evidence to demonstrate the efficacy of antibiotics in exacerbation or the role of shorter compared to longer durations of therapy and their associations with outcomes in nCFB exacerbations. An indirect comparative analysis of response at 7 and 14 days was conducted on a study of 53 patients receiving ciprofloxacin with or without tobramycin. When study arms were pooled, both microbiologic and clinical outcomes of bacterial load and forced expiratory volume in one second (FEV₁) were similar at day 7 and 14³¹. A study of 32 nCFB exacerbations identified that 14 days of intravenous antibiotics resulted in biochemical (C-reactive protein), microbiologic (bacterial clearance) and symptomatic improvements (24-hour sputum volume, incremental walk test) but did not result in spirometric improvement³². Similarly, another study of 34 patients treated for nCFB exacerbation with intravenous antibiotics for 14 days demonstrated attenuation of airway inflammation and bacterial load¹.

Consideration of optimal duration of therapy requires a balance of harm and benefit including short and longer-term effects including quality of life, subsequent exacerbations, and lung disease progression. It is possible to advocate for shorter courses of antibiotics for exacerbations in mild cases, less virulent or drug-resistant pathogens, or in those with rapid clinical responses²⁹. However, this raises a number of issues. Generally, pulmonary exacerbations are diagnosed on a basis of clinical and spirometric signs and symptoms and severe episodes are thought to require hospitalization and/or intravenous antibiotics. However, even though a consensus definition is available, no validated definition of exacerbation severity exists. Antimicrobial resistance and resistant pathogens are associated with a number of negative outcomes across a multitude of diseases^{33–35}, but it has also been demonstrated that antibiotic susceptibility, or using (*in vitro* predicted) active agents does not correlate with outcomes³⁶. A recent systematic review³⁷ and a cohort study³⁸ of CF both demonstrated that antimicrobial susceptibility testing (AST) did not correlate with pulmonary outcomes; notably, the pediatric cohort study identified that AST resulted in a greater odds of antibiotic switching³⁸. Additional issues to consider added to duration of exacerbation treatment include the antimicrobial agent, route, and number used for optimal therapy.

Treatment considerations for chronic management:

Chronic therapies in nCFB may be utilized to maintain or optimize pulmonary health, or prevent or reduce complications including pulmonary exacerbation episodes. For patients with frequent exacerbations (three events per year) or for those with chronic airways infection with *P. aeruginosa*, there is moderate quality evidence to recommend use of three or more months of antimicrobial therapies with inhaled antibiotics^{6,39–41}. Long-term therapy with macrolides have also been recommended in these patient groups (see below) instead of, or in addition to inhaled therapies based on infection status (*P. aeruginosa*), tolerance, feasibility and presence of contraindications^{6,29}. In certain cases, other oral antibiotics (i.e. penicillins⁴², tetracyclines⁴³) may also be used in place of inhaled therapies or macrolides for this purpose. Pooled, the limited evidence suggests that oral and inhaled antibiotics in these patient groups leads to decreased exacerbation frequency, delayed time to exacerbation, and improved respiratory symptoms (purulent sputum, breathlessness), but may increase adverse events and antimicrobial resistance^{6,44–47}.

Long-term macrolide use

Macrolide antibiotics (erythromycin or azithromycin) have been evaluated in three randomized controlled trials in regards to their effects on nCFB exacerbation frequency^{48–50}. The EMBRACE study examined 144 patients on azithromycin or placebo demonstrated a relative risk of 0.38 (95% CI 0.26–0.54) for the azithromycin group with patient-event rates of 0.59 and 1.57 respectively⁴⁸. The BAT study followed 83 patients on azithromycin or placebo over 12 months and similarly demonstrated a reduction in median exacerbation frequency with 0 (IQR 0–1) and 2 (1–3) in the two groups respectively⁵⁰. Lastly, the BLESS trial studied 117 patients on erythromycin or placebo over a 12 month period and noted a significant reduction in exacerbations (protocol defined) in the erythromycin group (1.29, 95% CI 0.93–1.65 versus 1.97, 95% CI 1.45–2.48)⁴⁹.

Long-term macrolide studies identified that diarrhea was the most common adverse event although this did not commonly lead to treatment discontinuation^{45,47}. Other potential adverse events attributable to macrolides including tinnitus, hearing loss, and QT prolongation are not well documented in nCFB but must be considered with long-term use. Notably, there was also a 28% and 88% increase in macrolide-resistant *Streptococci* following erythromycin and azithromycin use for 12 months respectively^{49,50}; this was not the case in trials using inhaled antimicrobials.

In the trials of long-term macrolides, few patients had *P. aeruginosa*, and the majority had a mean of three or more exacerbations in the pre-enrollment year^{48–50}. Thus, macrolides have been recommended as a first line therapy in those with frequent exacerbations, and without *P. aeruginosa*^{48–50}. However, long-term macrolides may be used as an adjunct or alternative agent in those with *P. aeruginosa* infection, and selection of this agent may also be influenced by other patient factors. As all of the studies have been 12 months, one must also consider the potential for attenuation of the effect after this period. In the nCFB studies, one study suggested a sustained benefit for six months following cessation of macrolide therapy⁴⁸, while another suggested lack of benefit in regards to exacerbations⁵⁰. A population-based cohort study of long-term azithromycin use in persons with cystic fibrosis

on inhaled anti-pseudomonals identified that the effects on lung function decline and pulmonary exacerbation risk attenuated over time⁵¹. Thus, long-term use of macrolides (or other antimicrobials) must be done with consideration of clinical effects balanced with costs, and risk of adverse effects over time.

Knowledge gaps and future directions

Expert consensus has long dominated the field of nCFB management. It is critical to understand the role and effect of antibiotic therapies (in conjunction with other pulmonary agents) in exacerbations, eradication of new pathogens, and in chronic management of persons with nCFB. Recent work in the field of CF has identified the significant gaps in our understanding of the diagnosis and management of pulmonary exacerbation events. This has led to the design and implementation of multi-center randomized pragmatic studies to elucidate the optimal management strategies (of which duration of therapy is a first priority) of CF pulmonary exacerbations^{52,53} (STOP2 –). Additionally, use of population-based registries in cystic fibrosis have enabled study of exacerbations, treatment practice patterns, and identifying key questions and priorities. Recently, a number of nCFB registries have been developed which will similarly allow for population-based studies and clinical trials including of pulmonary exacerbations²⁶ (PROGNOSIS –). Pragmatically designed studies in nCFB exacerbation management will be key to produce generalizable and directly applicable results to this patient population⁵⁴.

Conclusion

Management aspects in nCFB exacerbations remain poorly understood. Antibiotic duration for pulmonary exacerbations remains an expert consensus highlighting the need for well-designed studies of this important population. Importantly, there have been a number of clinical trials of recent antibiotic therapies in nCFB, and the development of registries which will enable population-based basic science and clinical studies. Rationally designed clinical trials will be critical to develop evidence-based approaches to antimicrobial use in the management of nCFB.

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