Using Cystic Fibrosis Therapies for Non–Cystic Fibrosis Bronchiectasis

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KEYWORDS

• Bronchiectasis • Cystic fibrosis • Non–cystic fibrosis • Chest medicine • Treatment

KEY POINTS

- Non–cystic fibrosis bronchiectasis is a significant cause of morbidity and mortality and its prevalence is increasing.
- A work-up must be initiated to determine the cause of the bronchiectasis but the etiology remains unknown in a significant percentage of cases.
- Unlike CF, adult non-CF bronchiectasis is a heterogeneous disease in regards to its cause, disease progression, and response to therapy.
- Hence, despite similarities in signs and symptoms, management of adult non-CF bronchiectasis cannot be routinely extrapolated from studies performed in patients with CF.

INTRODUCTION

Non–cystic fibrosis bronchiectasis (NCFB) is an increasingly prevalent disease in the United States and Europe. Its incidence increases with age, and peaks at ages 75 to 84.[1,2] NCFB is associated with longer hospital stays, more frequent clinic visits, more antibiotic use, and more extensive medical therapy than matched control subjects.[3] A review of 30 US health plans estimates that NCFB results in medical care expenditures of $630 million annually (2001 US dollars). Mortality is also increased, with an estimate of 10.6% in patients with NCFB over a 3.5-year observation period in a single study.[4] Many therapies used to treat cystic fibrosis (CF) are also used for patients with NCFB, with varying success. Unlike CF, however, NCFB is a heterogeneous disease, with a variety of predisposing factors and disease mechanisms implicated in its pathogenesis. This article explores the evidence for which therapeutic strategies used to treat CF have been translated into the care of NCFB. We conclude that therapies for adult NCFB cannot be simply extrapolated from CF clinical trials, and in some instances, doing so may actually result in harm.

PATHOPHYSIOLOGY

The "vicious cycle" hypothesis proposed by Cole[5] is the generally accepted explanation for the evolution of bronchiectasis. It is thought that airway damage resulting from a neutrophilic-dominant inflammatory response to infection, or tissue injury, leads to mucus stasis and predisposes to persistent infections thus perpetuating a "vicious cycle" of inflammation and damage.[5,6] Alternatively, endogenous innate immune deficiencies including ciliary dysfunction or immunoglobulin deficiencies, among many others, may initiate mucus stasis or

Disclosure Statement: The authors have nothing to disclose.
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Clin Chest Med 37 (2016) 139–146
http://dx.doi.org/10.1016/j.ccm.2015.11.005
0272-5231/16/$ – see front matter

changes in the airway microbiome. Airway bacterial colonization is facilitated by impaired neutrophil opsonophagocytic killing. Neutrophil elastase, released by activated neutrophils, can impair bacterial clearance by slowing ciliary beat frequency and promoting mucus hypersecretion.[7,8]

PATIENT EVALUATION

Causes of NCFB range from postinfectious to immune dysregulation (**Box 1**). The British Thoracic Society published guidelines for the evaluation of NCFB[9] (**Box 2**). However, the cause remains unknown in 10% to 53% of cases even after extensive evaluation.[10–12]

PHARMACOLOGIC TREATMENT OPTIONS

Pharmacologic and nonpharmacologic therapies are used in CF and NCFB with varying success. The differences in efficacy likely result from differences in pathophysiology and patient demographics. The major areas of therapy used in CF and their utility in NCFB are reviewed next.

Box 1
Etiologies of NCFB

- Autoimmune disease
  - Rheumatoid arthritis
  - Sjögren syndrome
- Primary ciliary dyskinesia
- Connective tissue disease
  - Tracheobronchomegaly (Mounier-Kuhn syndrome)
  - Marfan syndrome
  - Cartilage deficiency (Williams-Campbell syndrome)
- Allergic bronchopulmonary aspergillosis
- Immune deficiency
  - Human immunodeficiency virus
  - Immunoglobulin deficiency
  - Hyper-IgE syndrome
- Inflammatory bowel disease
- Previous infections
- Aspiration
- Smoke inhalation
- Malignancy
  - Chronic lymphocytic leukemia
  - Stem cell transplantation, graft-versus-host disease
- Obstruction (tumor, foreign body)
- α_1-Antitrypsin syndrome

Box 2
Historical and diagnostic evaluation of NCFB

Historical

- Neonatal symptoms
- Infertility
- Previous pneumonia
- Gastric aspiration
- Asthma
- Connective tissue
- Autoimmune symptoms

Diagnostic

- Sputum culture; bacteria/mycobacteria
- Pulmonary function testing
- IgA, IgE, IgG, and IgM
- Pneumococcal vaccine titers
- Sweat chloride test
- CFTR genetic analysis
- ANA, RF, aCCP, SSA, SSB antibodies
- α_1-Antitrypsin
- Ciliary ultrastructure

Bronchodilators

There is no definitive evidence that β-adrenergic or anticholinergic agents significantly improve outcomes in CF or NCFB.[13] Although bronchodilator therapies can potentially improve lung physiology and patient symptoms by improving mucociliary clearance, relieving bronchospasm, and reducing air-trapping, there is insufficient evidence to recommend regularly prescribing short-acting β_2-adrenergic agonists or anticholinergics for patients with CF or NCFB. These medications may be used safely if there is evidence of bronchospasm or air-trapping on pulmonary function testing, and continued if there is evidence for clinical improvement.[14,15]

Anti-inflammatory Therapy

The goal of anti-inflammatory therapy is to mitigate the airway remodeling, gas exchange abnormalities, and symptoms driven by inflammation without exacerbating airway infection or causing serious toxicity.

Corticosteroids

Theoretically, inhaled corticosteroids (ICS) may decrease airway inflammation without the increased