The Pathogenesis of Bronchiectasis

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KEYWORDS

• Bronchiectasis • Inflammation • Mucus • *Pseudomonas aeruginosa*
• Polymorphonuclear leukocyte

KEY POINTS

- Bronchiectasis is a condition with heterogeneous inciting factors that result in impaired ability to clear bacteria from the airways, perpetuating ongoing inflammation, and resulting progressive damage to the airways.
- Abnormal mucus clearance, from abnormalities in the mucus itself and/or impaired ability to clear otherwise normal mucus, is a common initiating factor that facilitates chronic bacterial airway infection.
- Direct inflammatory insults to the airway, from autoimmune-mediated inflammation, protease-antiprotease imbalance, to noxious agents, can incite airway damage that results in bronchiectasis.
- Once chronic airway bacterial infection is in place, the resulting inflammatory response and direct toxic substances elaborated by the bacteria promote further airway damage and resulting airway dilatation.

INTRODUCTION

Bronchiectasis is defined as permanent dilatation of the conducting airways and is generally associated with symptoms of persistent cough, usually productive of sputum and episodes of exacerbation characterized by several of the following: increased volume and/or purulence of sputum, shortness of breath, fatigue, chest pain, hemoptysis, fever, or cough.[1] In severely affected patients, progressive airways obstruction develops. However, the severity of bronchiectasis is varied, with some patients demonstrating permanent yet asymptomatic irreversible bronchial dilatation, whereas others have daily production of voluminous, purulent sputum, chronic infection with pathogens such as *Pseudomonas aeruginosa* (PA), and several exacerbations each year.

Histopathology of Bronchiectasis

Bronchiectasis was described by Laennec in 1819,[2] when it was most commonly seen as a complication of pulmonary tuberculosis. In 1950, Reid,[3] examining postmortem and surgical specimens, described the loss of bronchial subdivisions and 3 types of bronchiectasis—cylindrical, varicose, and saccular or cystic. These descriptions have been adapted to the radiologic chest computed tomographic (CT) imaging of bronchiectasis. Although these 3 manifestations do correlate with the degree of airway destruction and symptoms, they provide little insight into the pathophysiology of bronchiectasis. In 1952, Whitwell[4] published the findings of a histopathologic study of 200 operative specimens resected due to bronchiectasis. He described the loss of cartilage,

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muscle, elastic tissue, and in cystic bronchiectasis, of ciliated epithelium. He found lymphoid follicles, enlarged lymph nodes (which he thought contributed to airway obstruction in some cases), inflammation with peribronchial fibrosis, and interstitial pneumonia. Inflammation in the bronchial wall involved predominantly lymphocytes and macrophages, whereas polymorphonuclear leukocytes were predominant in the bronchial lumen.[5] Published in 1986, Cole's classic description of the vicious cycle of bronchiectasis[6] (Fig. 1A) has served us well, describing the role of chronic infection, resulting inflammation, impaired mucus clearance, and resulting airway damage, leading to disease progression. More recently, Flume and colleagues[7] proposed a vicious vortex model that more completely illustrated the complexity of the chronic infection and the reality that in many patients the relationship of these factors is not unidirectional (Fig. 1B). However, neither of these models provides a temporal basis/context for the origin of bronchiectasis in that neither identifies the initial events leading to disease. Indeed, there is not widespread

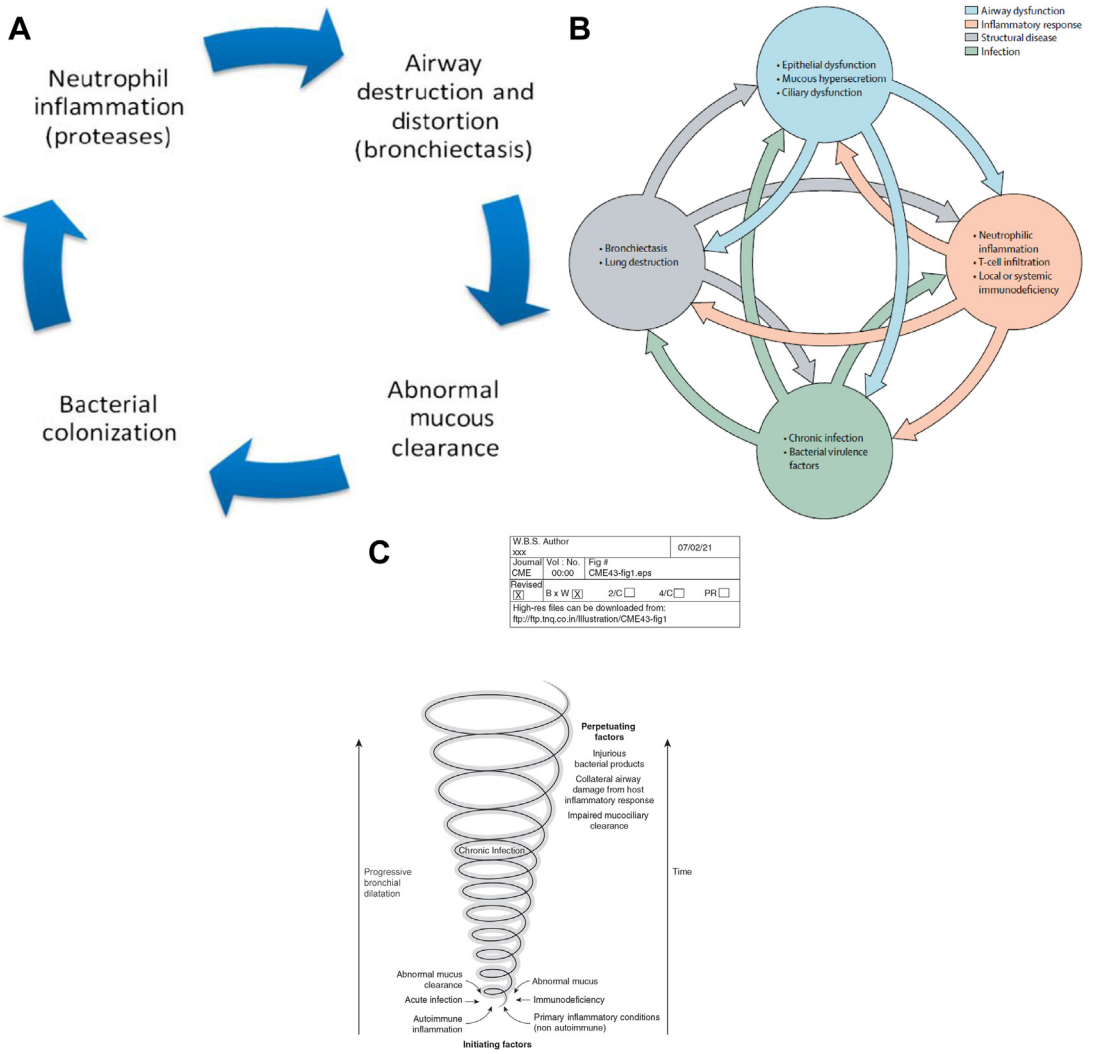

Fig. 1. (*A*) Cole's[6] vicious cycle of bronchiectasis pathogenesis. (*B*) Flume and colleagues'[7] vicious vortex of bronchiectasis pathogenesis. (*C*) A proposed alternative version of the vicious vortex of bronchiectasis pathogenesis. (*From* McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2013 Sep 15;188(6):647-56. Reprinted with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved; and [*B*] *From* Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet. 2018 Sep 8;392(10150):880-890. Reproduced with permission of Elsevier.)

agreement as to whether there is a clinically apparent precursor state to bronchiectasis in adults, or if there is one, what it looks like, although logic would dictate that there must be. However, some experts believe that the entity of protracted bacterial bronchitis (PBB) precedes the development of bronchiectasis in some patients and that the inflammation associated with persistent bacterial infection leads to the pathologic changes that result in airway dilatation. Although PBB and its putative relationship to bronchiectasis has most commonly been reported in children,[8] the recent report of several cases in adults who had underlying conditions known to cause bronchiectasis, and the observed progression from PBB to bronchiectasis in one of the cases,[9] lends credence to the suggestion that in at least some adults, PBB is a precursor to bronchiectasis.

The mechanism by which chronic inflammation of the airway wall leads to bronchial dilatation is not completely understood. The destruction of various components of the airway wall likely leads to loss of structural integrity, with weaker, more compliant airway walls and therefore, dilatation at least in part based on circumferential "traction" on the walls due to the elastic recoil of the surrounding lung parenchyma. Although the mechanism might be similar, this should not be confused with "traction bronchiectasis," in which abnormally increased elastic recoil of the lung due to interstitial disease results in dilatation of otherwise normal airways. Traction bronchiectasis usually does not result in clinically significant consequences. Other potential mechanisms for bronchial dilatation have been proposed, specifically, increased intraluminal pressure due to mucus plugging and chronic cough. These seem less likely to be important causes, given the lack of bronchial dilatation in the vast majority of patients who have chronic cough unassociated with chronic infection. Furthermore, it is not uncommon to discover an incidental finding of bronchiectasis in patients without significant cough or mucus plugging. Similarly, the frequent finding of bronchial dilatation even in relatively proximal airways that likely never had been completely obstructed mitigates against increased luminal pressure being the cause of dilatation in most cases. On the other hand, the common findings of proximal mucus plugging and bronchiectasis in allergic bronchopulmonary aspergillosis suggest that this hypothesis cannot be completely dismissed.

Building on the vicious cycle schema initially suggested by Cole,[6] (see **Fig. 1**A) refined by Flume and colleagues[7] to a vicious vortex reflecting the interrelationships of the contributing factors (see **Fig. 1**B), we offer an alternate representation of the vicious vortex. In doing so, we attempt to illustrate initiating factors and distinguish them from the perpetuating factors that continue to result in progressive airway damage, even in cases in which the initiating factor has resolved (**Fig. 1**C). **Table 1** illustrates some of the most common "causes" of bronchiectasis using this schema of initiating and perpetuating factors contributing to the development and progression of bronchiectasis.

INITIATING FACTORS

Although this section of the article lists several causes of bronchiectasis, it is not meant to be an exhaustive recitation of all its causes. Rather, our goal is to discuss the pathophysiologic mechanisms leading to bronchiectasis, using some of the most common underlying causes to illustrate these mechanisms. Readers will note that we depart from how various causes have been categorized by prior authors, to group causes based on their direct pathogenic effects on the airways. For example, although cystic fibrosis (CF), primary ciliary dyskinesia, and alpha-1-antitrypsin deficiency are commonly grouped together as "genetic causes," the mechanisms by which each results in bronchiectasis are completely different, as described later.

Abnormalities of Mucus

The production of normal mucus is crucial for the maintenance of airway and lung homeostasis. Mice lacking a gene necessary for mucus synthesis die of pulmonary inflammation.[10] Mucus creates a physical barrier that protects the airway epithelium from inhaled particles and toxins. Furthermore, glycoproteins, a major component of mucus, is rich in carbohydrate moieties, which provide binding sites for pathogenic bacteria, preventing binding to the respiratory epithelium. Mucous clearance, by either ciliary function or cough, promotes clearance of bacteria and potentially damaging inhaled substances. Given its importance, it is not surprising that the production of abnormal mucus can result in bronchiectasis. CF is the most well-known condition in this category, in which defects in the cystic fibrosis transmembrane conductance regulator (CFTR) results in defective ion transport, thereby causing the airway mucus to be dry and viscous. Although other mechanisms may also play a role, the water-deficient mucus leads to defective clearance, bacterial overgrowth, and chronic infection and inflammation.[11] Less well known is the epithelial sodium channel (ENaC), missense

Table 1
Initiating and perpetuating factors associated with common causes of bronchiectasis

Type of Factor	Specific Factor	Examples
Initiating factors	Impaired mucociliary clearance	Primary ciliary dyskinesia
		Anatomic airway obstruction
	Abnormalities of mucus	Cystic fibrosis
		ENaC mutations
	Infection	Tuberculosis
		Nontuberculous mycobacteria
		Acute pneumonia, measles, pertussis
	Autoimmune airway inflammation	
		Inflammatory bowel diseases
		Sjögren disease, rheumatoid arthritis, etc.
	Systemic immunodeficiency	
		Common variable immunodeficiency
		Lymphoma
		Immunosuppressive therapy
	Noninfectious (nonautoimmune) inflammatory states	
		Alpha-1-antitrypsin deficiency
		Gastroesophageal reflux?
		Toxic inhalation-ammonia, "mustard gas"
		Asthma, allergic bronchopulmonary aspergillosis, and chronic obstructive pulmonary disease[a]
Perpetuating factors	Any of the above-mentioned factors that persists	
	Bacterial products	
		Toxins
		Biofilms
	Host immune response	
		Cellular inflammatory products
		Proteases
	Abnormalities of mucus related to immune response	
		mucus hypersecretion
		Abnormal mucus due to products of inflammation
	Abnormal mucus clearance	
		Mucus plugging
		Functional airway obstruction
		Impaired ciliary function

Abbreviation: ENaC, epithelial sodium channel.
[a] It is unclear to what extent the airway inflammation associated with these conditions, the resultant development of mucus plugging, and/or the resulting airway bacterial infection drives the development of bronchiectasis.

mutations and polymorphisms of which can also lead to defective sodium transport and increased risk for bronchiectasis.[12]

Abnormalities of Mucus Clearance Mechanisms

The most common example of this risk is primary ciliary dyskinesia, which directly impairs mucociliary clearance, leading to retained mucus, chronic bacterial infections, and ultimately bronchiectasis in virtually every afflicted patient. Local airway obstruction from tumor or benign causes may also result in chronic infection and bronchiectasis. Williams-Campbell syndrome, a rare congenital condition manifested by lack of cartilage in the conducting airways might result in bronchiectasis due to the resulting severe airways obstruction, which could impair cough clearance.[13] It is unknown to what extent severe airways obstruction in asthma and chronic obstructive pulmonary disease (COPD) might lead to increased risk for

bronchiectasis by this mechanism, or whether other factors such as impaired local immunity or airway wall inflammation are more important. It is also thought that the lymphoid follicles noted by Whitwell[4] in pathologic specimens may contribute to small airway obstruction, leading to impaired mucus clearance and resulting chronic infection and inflammation.[14]

Acute infection

In many cohorts, "postinfectious" is the most commonly identified cause of bronchiectasis. In some cases, it is a distant childhood acute infection such as pertussis or measles that is blamed. It is often unclear the extent to which the infection is actually relevant to the bronchiectasis detected many years later, as opposed to a previously healthy child who develops chronic cough after an acute infection and is found to have bronchiectasis. Although bronchiectasis is commonly mentioned as a result of an acute bacterial pneumonia, there is limited literature supporting this being a frequent occurrence. In many patients who are found to have bronchiectasis after an acute lower respiratory tract infection, careful "sleuthing" reveals that the patient likely had preexisting bronchiectasis and the acute infection was a sequela of the bronchiectasis and not the cause. Although common in children, reversible airway dilatation after acute infection can also occur in adults.[15]

Chronic Infection

Bronchiectasis has been increasingly recognized in the setting of immunocompetent nontuberculous mycobacterial (NTM) infection, most commonly *Mycobacterium avium* complex (MAC). In identifying the potential causal direction of this association, there is a chicken-egg problem: does the MAC cause the bronchiectasis or does the bronchiectasis increase the risk for MAC, making it a complication of the preexisting bronchiectasis? There seems to be little doubt that bronchiectasis increases the risk for NTM,[16] similar to what is seen in CF; however, some patients seem to develop bronchiectasis in association with the MAC infection, not before.[9]

Systemic immunodeficiency

It is well known that systemic immune defects lead to bronchiectasis, almost surely by leading to impaired bacterial clearance, chronic bacterial airway infection, and the resulting inflammatory response; these may be purely genetic immunodeficiencies, such as X-linked agammaglobulinemia, or acquired defects such as most cases of common variable immunodeficiency. With these humoral immunodeficiencies, immunoglobulin replacement leads to improved quality of life and reduced exacerbation rate, directly linking the antibody deficiency to the manifestations of airway infection. Defects of cell-mediated immunity such as in association with some hematologic malignancies and/or their treatment can also lead to bronchiectasis. The relationship between bronchiectasis and innate immune deficiency, specifically mannose-binding lectin deficiency, is more complex. Studies have not found a direct association between mannose-binding lectin deficiency and the occurrence of bronchiectasis, although the severity seems to be increased when it occurs.[17]

Autoimmune disease

Several autoimmune diseases that predominantly target other areas of the body may result in airway inflammation with a continuum of manifestations that may be limited to chronic cough or bronchiolitis but also includes bronchiectasis. The most common autoimmune diseases that result in bronchiectasis appear to be rheumatoid arthritis, Sjögren disease, ulcerative colitis, and Crohn disease. It is unknown whether chronic inflammation directly due to the autoimmune disease is the initiating factor for the development of bronchial dilatation. The other possibility is that the perturbed environment due to the autoimmune-mediated inflammation affects local host defenses, resulting in chronic infection. Although we are not aware of supporting data, it is the authors' clinical impression, as well as that of other experts, that many of these patients are symptomatic despite not having evidence of bacterial infection. Not unexpectedly, dry cough, as opposed to cough productive of purulent secretions, seems to be more common in these patients. Also, supporting the importance of autoimmune-related inflammation driving at least some of the symptoms, immunosuppressive therapy such as corticosteroids or anti-tumor necrosis factor (TNF) agents directed at the underlying condition may decrease the cough and even decrease exacerbation rates.[18]

Asthma and Chronic Obstructive Pulmonary Disease

Both of these airway diseases predispose to bronchiectasis, because it is seen in higher percentages than among the general population. In many patients, the bronchiectasis seems to be an incidental finding, with mild bronchial dilatation, but no clinical manifestations that distinguish these patients from the typical patient with asthma or COPD. Furthermore, in some patients with COPD with apparent airway dilatation, that appearance is actually due to narrowing or pruning

of the pulmonary artery and not dilatation of the bronchi.[19] Nonetheless, in some patients the bronchiectasis is clinically significant, with accompanying chronic airway infection by organisms not typically seen in asthma or COPD. These patients tend to have more severe asthma and COPD than patients who do not develop bronchiectasis.[20,21] Of course, bronchiectasis is also a feature of allergic bronchopulmonary aspergillosis. It is unknown whether the chronic inflammation and mucus plugging associated with these conditions leads to perturbation of local host defenses and then chronic airway infection, or whether a different mechanism, such as the mechanical effect of airways obstruction, plays a role.

Noninfectious Inflammatory States

Patients with homozygous alpha-1-antitrypsin PiZZ deficiency have uncontrolled excessive protease activity that results in emphysema in some patients, especially cigarette smokers. These patients are also at high risk of developing bronchiectasis, with 27% in one cohort of ZZ patients having clinically significant bronchiectasis.[22] Inhalation of directly acting irritant substances may result in damage to the airways and resulting bronchiectasis; these include inhalational injuries from industrial accidents with ammonia[23] and the chemical warfare agent, "mustard gas."[24] Gastroesophageal reflux is more common in patients with bronchiectasis than in the general population, and direct acid injury of the airway may be a factor in this association; however, this is not yet clear, and the relationship might be more complex.[25] In one rat model, intratracheal nitric acid instillation resulted in several types of airway lesions, including bronchiectasis.[26] Bronchiectasis has also been reported as a common sequela of bronchial thermoplasty.[27]

Double-Hit Hypothesis

There are several relevant genetic mutations that do not seem to directly cause bronchiectasis in heterozygotes or in those with milder mutations, because the vast majority of such patients never develop disease. However, these genetic abnormalities are seen with greater frequency in patients with bronchiectasis than in individuals without bronchiectasis, suggesting that they may contribute to its pathophysiology; these include heterozygotes with a single CFTR mutation,[28] patients with milder alpha-1-antitrypsin mutations, or those heterozygote for the Z allele.[29] The finding that coexisting single CFTR mutations and ENaC mutations increase the risk of bronchiectasis[12] also supports this hypothesis. One theory that could explain these findings is that these abnormalities, alone, are not sufficient to cause bronchiectasis, but they increase the susceptibility in patients who have an additional risk factor, whether it be another as yet undiscovered genetic abnormality or other intrinsic or environmental factors, with these factors serving as a "second-hit." This phenomenon is nicely demonstrated by the interaction of common variable immunodeficiency (CVID) and deficiency of mannose-binding lectin. Bronchiectasis is more common in patients with CVID with mannose-binding lectin deficiency than in those without,[30] but among the general population, patients with mannose-binding lectin deficiency are no more likely than normals to develop bronchiectasis.[17] In this case, "the exception may prove the rule," as patients with mannose-binding lectin deficiency who do develop bronchiectasis tend to have more severe disease than those without deficiency.[17] Similarly, patients with rheumatoid arthritis who have a single CFTR mutation are more likely to have bronchiectasis than patients with rheumatoid arthritis who have normal CFTR.[31]

PERPETUATING FACTORS

Mucociliary Clearance

The perpetuation and progression of bronchiectasis, including the often-frequent exacerbations and tissue destruction, is due to a complex combination of an uncontrolled inflammatory response, chronic infection with potentially virulent bacteria, impaired mucociliary clearance, and resistance to antibiotics.[32] This section examines each of the factors. As will be emphasized, almost every cell and secretory component has salutary effects on bacterial killing and removal, but excessive amounts or ineffectual clearing may also damage airway and lung tissue.[33]

Neutrophils and Neutrophil Elastase

Normal airway secretions contain 95% macrophages. In bronchiectasis, the predominant cell is the neutrophil. Bacteria attract neutrophils via a variety of released chemokines including interleukin (IL)-8, IL-1, and TNF-alpha. Upon mobilization to sites of infection, neutrophils release potent enzymes including elastase and myeloperoxidase. Neutrophil elastase (NE) is a 29-kDa serine proteinase stored in neutrophil granules and released into neutrophil extracellular traps (NETs) or at times of apoptosis. NE is highly inflammatory and a potent neutralizer of bacteria. NE also impairs ciliary motility and stimulates mucus secretion. NE is neutralized by serum-derived alpha-1 antitrypsin, secretory leukoproteinase

inhibitor, and epithelial cell-derived syndecan-1. NE is the main culprit causing alveolar damage via destruction of elastin in COPD, including alpha-1 antitrypsin deficiency. Studies have found very high levels of NE in the sputum of patients with CF and bronchiectasis.[34]

In a single-center study from Scotland, higher sputum levels of NE highly correlated with disease severity, categorized by impairment of pulmonary function or forced expiratory volume in the first second of expiration (FEV_1), scores on St. George's Respiratory Questionnaire and the Bronchiectasis Severity Index (BSI), and extent of bronchiectasis on chest CT by the Reiff score. High levels of NE also correlated with the presence of and quantity of pathogenic bacteria including PA and other gram-negative bacteria. During longitudinal assessments, individuals with the highest levels of NE had increased frequencies of exacerbations and shorter time to any subsequent exacerbation, but not mortality. In a small subset of 26 patients with exacerbations, sputum NE increased from baseline at the beginning of an exacerbation, decreased at the end of 2 weeks of antibiotic administration, but remained at a higher level than baseline sputum NE 6 months after resolution of the exacerbation.[35]

Interest in NE as a biomarker and proinflammatory mediator has been heightened with the recent phase 2 results of the study of the oral drug, brensocatib, an inhibitor of dipeptidyl peptidase-1, also known as cathepsin C (the enzyme that activates serine proteases). Brensocatib treatment prolonged the time to first exacerbation and reduced the number of exacerbations compared with placebo. Sputum levels of elastase were significantly lower in the brensocatib-treated subjects, supporting the role of NE in the pathophysiology of bronchiectasis.[36]

Neutrophil Extracellular Traps and Neutrophil Zone Protein

Pregnancy zone protein (PZP) is a glycoprotein found mainly in the cytoplasm of PMNs and also eosinophils. PZP has broad immunosuppressive and antiprotease properties. PZP was originally found in pregnant women and thought to prevent fetal rejection. PZP is one of the products extruded from neutrophils as part of the NET formation. NETs trap and neutralize pathogens (also elastase and myeloperoxidase). Recently PZP has been found to be elevated in the sputum (not blood) of patients with bronchiectasis. PZP is not found in airway epithelial cells, and only low levels are found in monocytes. NETs are intriguing because there is evidence that like NE, they may reduce bacterial infection but may allow tissue destruction.[37]

Elevated levels of PZP were found in patients with bronchiectasis who had worse severity as measured by the BSI, exacerbation rate, and the presence of PA. In patients who had an exacerbation with an increased quantitative bacterial load, PZP levels increased. After antibiotic administration sputum PZP levels declined. Another finding was that analysis of the microbiota by 16S ribosome sequencing showed high levels of PZP in the sputum of patients with common virulent pathogens including PA, *Stenotrophomonas*, and *Staphylococcus aureus* (SA) and lower levels in patients with *Streptococcus, Haemophilus,* and *Veillonella.* These data suggest PZP is a marker of enhanced inflammation, but it is not yet clear whether it contributes to the ongoing airway destruction or is merely a marker.[38]

Macrophages

After contact with an airway irritant, macrophages recruit neutrophils by release of IL-8. Macrophages are key components of phagocytosis and bacterial clearance via opsonizing antibodies and nonopsonizing mechanisms. PA via quorum sensing (QS) interferes with this clearance via release of virulence factors including pyocyanin. These virulence factors also neutralize humoral antibodies and interfere with ingestion of PA into macrophages.

Lymphocytes

Lymphocytes are also recruited to the airway. QS interferes with this recruitment as well as the formation of the key bronchus-associated lymphoid tissue (BALT), a component of innate immunity. BALT provides a major secondary reinforcing defense via dendritic cells ingesting invasive bacteria. BALT recruits both B and T lymphocytes that are directly responsible for the immune response to invasive bacteria. Animal models have demonstrated that a tardy or ineffective BALT immunity contributes to lung injury and mortality.[39]

Eosinophils

Blood and sputum eosinophils play a role in the major obstructive lung diseases, asthma and COPD.[40] Emerging evidence is accumulating that they may be a biomarker indicating a role for specific treatments.[41] Lung tissue attraction of eosinophils is stimulated by IL-5 and to a lesser extent IL-4, IL-13, and chemokines where they release major basic protein, a toxin to bronchial epithelial cells. Other eosinophilic proteases are found in excess in airways (sputum) of patients with

obstructive lung disease.[42] Emerging experience in bronchiectasis suggests that inhaled corticosteroids and IL-5 antagonists may play a role in reducing eosinophilic presence in some patients with bronchiectasis with blood eosinophilia.

Airway Epithelial Cells

Bronchial epithelial cells and overlying mucin provide the major physical, immune, and chemical protective barrier against microbe invasion. This barrier can be disrupted by physical trauma such as an endotracheal tube or suctioning, chemical insults such as acid aspiration, or chronic infection in bronchiectasis. Bacteria (PA, the most virulent) interacts with epithelial cells by attaching to mucins and cell surface receptors via flagella and pili. PA directly injects effector molecules that allow internalization.[43] QS signaling molecules directly break down mucins and stimulate mucus production and slow the coordinated beating of cilia, contributing to ineffective bacterial clearance. Yet, epithelial cells resist infection by secreting lactoferrin and enzymes that interfere with bacterial biofilm formation and allow entry of inflammatory cell cytokines and chemokines to attack virulent bacteria.

Mucociliary Clearance

Transport occurs by a combination of coordinated ciliary beating and cough. The mucociliary system protects the respiratory system (upper and lower airways) from noxious inhaled substances by trapping deposited particles and clears invading pathogens via an elaborate transport process. Mucus that lines epithelial surfaces is composed of an aqueous component (98% water), ions, glycoproteins, and mucin macromolecules, primarily the mucin polymers, MUC5B and MUC5AC. In bronchiectasis the gelatinous component and inflammatory debris are increased, leading to the trapping of bacteria, and also impairing transport, thereby leading to airway obstruction, and mucus plugging. Mucins consist of a viscoelastic gel produced by epithelial surface secretory cells and submucosal glands connected to the lumen by ciliary ducts. In airway diseases, mucin production and secretion is stimulated by infectious and other noxious agents, reducing elasticity. The higher mucin concentration augments the osmotic load, increasing competition for water with the aqueous layer, contributing to epithelial surface dehydration.[44] Less elasticity of the mucin overlying ciliary cells reduces proximal transport and loss of beating coordination. Expectorated sputum in patients with bronchiectasis contains inflammatory debris (DNA, neutrophils and NETs) and bacteria, exhibiting the almost pathognomonic 3-layered sputum that is observed when sputum is collected in a vessel.

There are therapeutic implications of the aqueous dehydration, as the administration of nebulized normal or hypertonic saline may assist rehydration in addition to a mechanical action of loosening tenacious adherent mucus plaques from epithelial surfaces. The drug DNase or dornase alpha that breaks down the increased DNA in vitro and in patients with CF does not improve clinical outcomes in non-CF bronchiectasis.[45]

Bacteria

The bacterial flora in bronchiectatic airways are different from those in asthma and COPD. In individuals with bronchiectasis and bacteria present in sputum cultures, PA and *Hemophilus influenza* are each present 25% to 30% of the time, SA and *Streptococcus pneumoniae* each 9% to 12%, and *Moraxella catarrhalis* 5% to 8%. PA is the most virulent, contributing to increased morbidity, accelerated decline in FEV_1, increased exacerbations and hospitalizations, and mortality.[46,47] The presence of PA is considered to represent infection and never a saprophyte or commensal. Although bacteremia does not usually occur in bronchiectasis, even during exacerbations, the invasion of epithelial cells by bacteria and endotoxins allows release of cytokines into the circulation that contributes to the systemic manifestations including fever, chills, rigors, excessive fatigue, and even pleuritic chest pain. PA virulence factors is discussed in detail.

Pseudomonas

PA is fascinating and very complex with a variety of injurious endotoxins and exotoxins, and one of the most invasive and damaging airway and sometimes systemic pathogens. PA rarely infects an immunocompetent host without structural lung damage, rather PA infection most often occurs in the setting of a systemic compromise such as severe burns, diabetes mellitus, organ transplants, or cancer as examples. In lung disease, PA requires a damaged airway with breaks in the epithelial mucosal barrier, altered local or systemic immunity, and often a host that has received multiple, prolonged, and/or often broad-spectrum antibiotics. These factors are present in the patient with bronchiectasis. Other respiratory diseases prone to PA infection have similar characteristics including CF, ventilator-associated pneumonia, and advanced COPD.[48]

PA is a gram-negative rod, facultative aerobe that adheres to airway epithelium via a single

flagellum, pili, and components of the outer plasma membrane. Flagella home into damaged epithelial cells via released glycophospholipids. For this adherence, there needs to be a breach in tight junctions or focal concentrations of the bacteria, both present in bronchiectasis.[49] Bacteriophages specific for each bacteria interfere with this adherence and reduce inflammation. Bacteriophages, because of actions against toxins including pyocyanin and lipopolysaccharide (LPS) may be an emerging alternative or adjunctive treatment of PA infection, in addition to antibiotics.[50]

The outer membrane of PA exhibits low permeability because of the expression of porins and lipoproteins. This outer membrane containing porin F provides resistance to influx of solutes and small molecules such as antibiotics. PA internal efflux pumps also externalize antibiotics that enter the bacteria. Key components of a bacteria's virulence is their secretory system, expressing factors directly into cells or the airway space. Potent exotoxins include proteases such as elastase and lipases that can be efficiently injected into epithelial cells. The outer membrane also contains LPS, an important PA virulence factor that upon release is partly responsible for the systemic symptomatic manifestations of PA infection.

Quorum Sensing

QS is a form of bacterial cell-to-cell communication that regulates gene expression and through a series of biochemical reactions induces the production of several of the virulence factors including proteases, pyocyanin (is also a pigment that provides the blue-green color to PA in culture), and LPS. In essence, QS allows bacteria to limit expression of certain genes to times when there is a high-enough population of bacteria that such expression will be beneficial (eg, biofilm or toxin production). QS and the ability to sense and respond to the environment and development of biofilms are fundamental to the initiation, propagation, and maintenance of PA.

Biofilms

Biofilms are structured and organized communities of bacteria (PA) surrounded by an extracellular polymeric matrix that provides stability and resistance against surrounding host defense cells, proteins, and antimicrobial agents. This surrounding matrix is composed of polysaccharides, lipids, proteins, and DNA produced by the bacteria. Biofilms enhance the bacterial virulence through QS communications. Antibiotic resistance is partially due to lack of penetrance of antimicrobials through biofilms. Other factors contributing to antibiotic resistance inside biofilms include the relative lower metabolic activity of PA and the low oxygen environment. QS and subsequent biofilm formation may be reduced with several natural compounds including ajoene (in garlic), iberin (horseradish), and eugenol (clove). No large clinical studies have been accomplished with these agents. Chronic macrolide antibiotic administration is the only management strategy that has been proved to reduce exacerbations in bronchiectasis. In addition to reducing neutrophilic inflammation, other mechanisms may be downregulating or inhibiting QS and biofilm formation.[51,52]

Staphylococcus aureus

Individuals with CF were originally thought to have a predominant SA microbial load and later acquired PA. More recent studies with quantitative cultures of sputum suggest that in adults both SA and PA coexist and contribute to worse outcomes than either organism alone. In contradistinction to CF, in bronchiectasis methicillin-resistant SA may not be a more virulent pathogen than methicillin-sensitive SA as evidenced by the rate of decline in FEV_1 and exacerbations.[53]

Microbiome

Traditional microbiologic cultures usually identify gram-negative PA, *H influenza,* and pathogens among others; however, they may miss fastidious potentially pathogenic bacteria. Anaerobic cultures are rarely performed. Quantitative bacterial cultures offer some advantages, but they are not readily available and their utility in sputum versus bronchoscopic lavage has been controversial. Newer molecular methodologies have emerged to help focus targets for antimicrobial management. The most straightforward definition is that the microbiome encompasses all the microorganism-derived genetic material in an environment. The microbiome methodology used most frequently in bronchiectasis to date is 16S ribosomal RNA amplicon sequencing. Key phyla identified included Proteobacteria (including *Pseudomonas and Haemophilus*), Firmicutes, and Bacteroidetes. The microbiome of the healthy airway is much different than in the bronchiectatic airway. In bronchiectasis there is altered mucociliary clearance and often dilated and tortuous airways with pockets allowing harboring of bacteria that may not be easily captured in large-enough quantities for traditional culture techniques. Because microbiome studies allow identification of genetic material from all species and an inability to quantitate the number of organisms, the utility will depend on trends and relevance of

organisms identified in stable versus exacerbation clinical states. Although this analytical technology is not new, only recently have trends emerged that may offer insights beyond traditional culture techniques.

The earliest studies of microbiome research confirmed the dominant presence of the genera *Pseudomonas* and *Haemophilus.* A recent study of 29 patients followed for 16 years showed by 16S ribosome amplicon sequencing relative stability of *Pseudomonas* and *Haemophilus* diversity (alpha diversity is a term referring to the abundance, richness, or number of species identified in a specimen), similar to culture-based studies.[54] During exacerbations, studies using microbiome analysis have demonstrated mixed conclusions with some studies showing minor changes in diversity and others showing major alterations. Regarding the severity of bronchiectasis by degree of impairment or declines in FEV_1, lower diversity of organisms is associated with more severe impairment. Larger and longitudinal studies, standardization of microbiome technology, and a better understanding of what happens during an exacerbation including any modification by antibiotics will be needed before microbiome sequencing can play a role in clinical practice.

SUMMARY

Because bacteria have an enormous capability to adapt to and modify their environment, a multimodal and perhaps continuous or lengthy approach to eradication or even suppression will be needed. Reliance on antibiotics alone and even regional delivery by inhalation has not been satisfactory and has engendered multidrug resistance. Production of antibodies or agents to modify production of virulence factors, and QS signals, as well as bacteriophages, and modified or newer antibiotics in addition to stabilizing the epithelial barrier will be important steps to reduce perpetuation of chronic infection in bronchiectasis. Drugs that inhibit serine proteinase activity also hold promise as a complementary strategy to shorten or reduce exacerbations. Although mucokinetic inhaled or oral agents have yet to demonstrate efficacy in bronchiectasis, addressing altered mucociliary clearance will be another therapeutic consideration.[31]

DISCLOSURE

Dr M.L. Metersky has served as a consultant for Insmed, Zambon and International Biophysics and has served as an Investigator in a clinical trial sponsored by Insmed. Dr A.F. Barker has no financial conflicts of interest to report.

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