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13.1 Introduction

Bronchiectasis, a heterogeneous disease, is characterized by a vicious cycle of airway infection and inflammation that results in structural damage to the airways and the surrounding lung parenchyma [1]. Many microorganisms have been associated with bronchiectasis, both as a complication of the anatomic abnormalities and possibly as a cause of the structural disease as well [2, 3]. Diverse polymicrobial communities are present in the airways of patients with bronchiectasis [4]. Studies using standard microbiologic culture techniques have demonstrated the presence of bacterial, fungal, and viral pathogens in the lungs of bronchiectasis patients both when the patient is clinically stable and when there is an exacerbation of disease [2, 5]. Newer molecular techniques have broadened our understanding of the microbiome in bronchiectasis patients [4, 6]. *Pseudomonas aeruginosa* has been repeatedly shown to be a problematic pathogen in patients with bronchiectasis and is associated with a worse prognosis [7, 8]. Multiple epidemiologic reports have shown that approximately 20–35% of patients worldwide with bronchiectasis are chronically infected with *P. aeruginosa* [2, 9, 10]. Several antibiotic trials have been published where the main target of therapy is *Pseudomonas aeruginosa* [11–17]. (See Chap. 11 for a full review of *P. aeruginosa* infections associated with bronchiectasis.) Another problematic group of pathogens, nontuberculous mycobacteria (NTM), is a common infecting organism in bronchiectasis, particularly in the United States and in parts of Asia [2, 18]. NTM infection is fully discussed in Chap. 13. In this chapter, we will review the role of bacterial pathogens other than *P. aeruginosa* and the impact of fungal and viral infections in bronchiectasis patients. (See Table 13.1.)

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Table 13.1 Bacteriology of bronchiectasis

	Nicotra et al. [10] 1995 (n = 123)	Pasteur et al. [9] 2000 (n = 150)	King et al. [19] 2007 (n = 89)	Aksamit et al. [2] 2016 (n = 1406)
<i>H. influenza</i> (%)	30 (24)	35 (23)	47 (53)	116 (8)
<i>M. catarrhalis</i> (%)	2 (2)	20 (13)	8 (9)	20 (1)
<i>S. pneumoniae</i> (%)	11 (9)	13 (9)	7 (8)	49 (3)
<i>S. aureus</i> (%)	7 (6)	14 (9)	4 (4)	170 (12)
<i>P. aeruginosa</i> (%)	31 (25)	31 (21)	12 (13)	470 (33)
<i>Mycobacteria</i> (%)	17 (14)	0 (0)	2 (2)	657 (50)
No organism (%)	Not specified	23 (15)	21 (24)	93 (7)

13.2 General Comments

Clinical and radiographic features in bronchiectasis are generally not specific enough to predict which microbial pathogen may be present. Age and overall severity of disease have been evaluated as possible markers for specific infections but are not sufficiently specific to pinpoint the infecting organism. In one series from Israel, younger patients (less than or equal to 64 years) with bronchiectasis were shown to be more likely infected with *Haemophilus* and older patients with *Pseudomonas* and *Enterobacteriaceae* [20], but this has not been seen in other large patient cohorts. Although patients with more severe disease (based on severity scores) are more likely to have chronic *Pseudomonas* infection, other pathogens may be present and be responsible for the patient's symptoms. Radiographic patterns of disease are also not sufficiently specific for identifying the infecting organisms. Although "tree-in-bud" nodularity is frequently thought to be diagnostic of NTM infections, recent studies have shown that the "tree-in-bud" finding simply represents endobronchial inflammation not specific to a particular organism [21, 22]. Sputum color charts developed in an attempt to correlate degree of sputum purulence with specific organisms have not been reliable in predicting culture results [23, 24]. Hence, it is imperative that sputum cultures be performed in all bronchiectasis patients on a regular basis in order to target treatments and assess prognosis.

13.3 Gram-Negative Bacterial Infections (Other than *P. aeruginosa*)

The most common bacterial organism reported in many epidemiologic series is *Haemophilus influenzae*. Thirty percent or more of patients with bronchiectasis are chronically infected with *H. influenzae* [9, 10, 19]. As with all bronchiectasis patients, the cornerstone of therapy for patients infected with this organism is airway clearance by various modalities, including mechanical, pharmacologic, and exercise [25–27]. When patients infected with *H. influenzae* have exacerbations, there are multiple oral antibiotics that can be used to treat the flares of infection. Institutional specific susceptibility patterns and patient tolerance should dictate the specifics of therapy. Maintenance inhaled antibiotics are generally not recommended for patients who are chronically infected with *H. influenzae*. One study of long-term inhaled

gentamicin, which included a few patients with chronic *H. influenzae* infection, did show benefit and reasonably good tolerance [13], but studies that used maintenance aztreonam for inhalation had negative results [15]. Chronic macrolide therapy may be appropriate for frequent exacerbators as long as there is appropriate attention for potential adverse effects [28]. (See Chap. 16 for a full review of macrolide therapy.)

Other Gram-negative organisms that are occasionally isolated from patients with bronchiectasis include *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Achromobacter*, *Alcaligenes*, *Serratia marcescens*, and *Escherichia coli*. Routine culturing of respiratory secretions is necessary in order to track the specific infecting organism in a particular patient. It is vital to target antibiotic therapy at that organism and to keep abreast of the antibiotic susceptibility pattern, which may change over time. There is insufficient data and no consensus on using maintenance antibiotics in patients infected with the above Gram-negative organisms. Expert opinion suggests that such therapy (by inhalation and targeted to the organism) may be useful in specific patients who have frequent exacerbations (greater than 2–3 per year that require systemic therapy) and/or in patients who have bothersome daily cough with a large volume of secretions. There is no specific guidance available regarding possible “eradication” therapy for Gram-negative infections with organisms other than *Pseudomonas*. (See Chap. 11 on chronic pseudomonas infections.)

13.4 Gram-Positive Infections

Staphylococcus aureus and *Streptococcus pneumoniae* are the Gram-positive organisms most frequently seen in bronchiectasis patients. In the US Bronchiectasis Registry, approximately 12% of patients had sputum cultures positive for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains) and 3% for *S. pneumoniae* [2]. Treatment of patients with these infections includes the usual airway clearance modalities and targeted antibiotic treatment. There are no data available for maintenance inhaled antibiotics for patients chronically infected with Gram-positive organisms. As with Gram-negative infections, there may be a role for targeted antimicrobial suppressant therapy for patients with frequent exacerbations and/or significant and bothersome day-to-day symptoms. Chronic macrolide therapy may have a role, but worrisome resistance may develop, particularly when the infecting organism is *Streptococcus pneumoniae*. The 2010 British Thoracic Society guidelines suggest that an eradication strategy might be considered in methicillin-resistant *S. aureus* infection when the organism is first identified although this recommendation is not based on any randomized controlled trials [27].

13.5 Nontuberculous Mycobacterial Infections

Up to 60% of US patients in specialized bronchiectasis centers are infected with NTM organisms [2]. *Mycobacterium avium complex* and *Mycobacterium abscessus* are the most frequently identified organisms. Not all patients require antibiotic

therapy for these infections; the decision to treat with antibiotics should be guided by the ATS/IDSA guideline published in 2007. (See Chap. 13 for a further discussion of NTM infections in bronchiectasis.)

13.5.1 *Nocardia/Actinomyces/Streptomyces* Infections

There is little data on the frequency of these infections in patients with bronchiectasis. The US Bronchiectasis Registry reported a very small number of patients whose respiratory cultures grew *Nocardia* [2]. The decision to proceed with antibiotic treatment targeting *Nocardia* or similar species should be based on repeatedly positive cultures in the absence of another pathogen that might be responsible for the patient's symptoms.

13.6 Normal Respiratory Flora

It is not unusual for a patient with bronchiectasis to culture only "normal oropharyngeal" flora from respiratory secretions. To some extent, this may represent the limitation of routine culture techniques in identifying the infecting organism in some patients with bronchiectasis in addition to the difficulty some patients have with producing sufficient sputum for laboratory processing. One small study in 33 Greek patients with bronchiectasis sought to identify whether *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or respiratory syncytial virus (RSV) might be present in bronchoalveolar lavage specimens; the findings were essentially negative [29]. New research into understanding the respiratory microbiome (see below) may help our understanding of what other organisms may be playing a role in the symptoms associated with bronchiectasis.

13.7 Fungal Infections

Aspergillus and *Candida* are commonly found in the respiratory secretions of patients with bronchiectasis; approximately 20% of patients in the US Registry had cultures positive for aspergillus [2]. A cohort of patient reported from Spain showed small numbers of patients had persistent culture positivity for *Aspergillus* (8.7%) and *Candida* (34.5%) [30]. It can be difficult to determine if these organisms are playing a role in the infectious symptoms or are simply bystander organisms in patients with other primary pathogens. Treatment aimed at *Aspergillus* should be considered if the patient has persistently positive cultures without another organism that might be culpable [31]. *Candida* rarely requires treatment as it is usually an oral contaminant. It is important to identify patients with the syndrome of allergic bronchopulmonary aspergillosis that can cause bronchiectasis; this immunologic disorder is distinct from secondary infection due to aspergillus.

13.8 Viral Infections

The role of viral infections in bronchiectasis is unclear with little data available on whether patients may be chronically infected with viruses or what role viruses have in triggering exacerbations. In a cohort of 119 Chinese adults with bronchiectasis, respiratory viruses were found more frequently by molecular testing from nasopharyngeal swabs and sputum samples when the patients had exacerbations of symptoms as compared to the stable state [5]. The most commonly identified viruses were *Coronavirus*, *Rhinovirus*, and *Influenza A* and *B*. RSV has also been found in bronchoalveolar lavage (BAL) specimens of patients with exacerbations of their bronchiectasis symptoms [29]. Seasonal variability of exacerbations in bronchiectasis has also been postulated to be due to viral exposure. Patients with bronchiectasis exacerbations may benefit from screening for viral infection, particularly in influenza season. Yearly vaccination against influenza is also recommended for all patients with bronchiectasis.

13.9 Future Directions

We are on the cusp of learning more about the polymicrobial communities present in the lungs of patients with bronchiectasis thanks to research on the respiratory microbiome. Studies to date have shown that aerobic and anaerobic bacteria are present in patients with stable-state bronchiectasis and when the patient is clinically exacerbated [4]. Emerging pathogens that may have a role in bronchiectasis exacerbations, including *Pandoraea* and *Ralstonia* species, have been identified [6]. The microbiome in bronchiectasis patients may vary according to the region in which the patient lives as well as due to antibiotic treatments and diet [32]. The degree of airway and systemic inflammation may be affected by the predominant bacterial taxa in the microbiome [33]. Finally, the ecology of the microbiome may be significantly affected by chronic therapies such as oral macrolides [34, 35]. We have much to learn from further investigation into the microbiome of patients with bronchiectasis which may inform treatment decisions. Though Tunney's study showed a surprising degree of stability in the microbial load and community composition before and after treatment of an exacerbation [4], Rogers et al. showed that long-term erythromycin changes the composition of the respiratory microbiota in patients with bronchiectasis [33]. Hence, close attention to the burgeoning literature on this area of investigation is needed for clinicians caring for patients with bronchiectasis.

Conclusions

Microorganisms other than *Pseudomonas* have a significant impact on patients with bronchiectasis. Our understanding of the wide spectrum of bacteria that infect these patients, including NTM, is growing. We know less about the impact of fungal and viral pathogens on the bronchiectatic lung. The impact of coinfection with multiple organisms is also poorly understood, especially with regard to which organism to target with specific antibiotic treatment. Current clinically available microbiologic

techniques do not provide a full understanding of the microbiologic diversity within the lungs of bronchiectasis patients. We may learn more from ongoing research into the lung microbiome as well as the impact of antimicrobial therapies on the balance of organisms within that microbiome. At the present time, it is imperative for clinicians to carefully monitor the microbiologic results of patients with bronchiectasis in order to provide optimal and judicious antibiotic treatments as well as to help with assessing the prognosis of the individual patient. The frequency of monitoring for each type of pathogen (routine bacterial, mycobacterial, viral, fungal) has not been clearly spelled out in existing guidelines. How sputum samples are handled (collection and processing) also varies from region to region and from laboratory to laboratory. In patients with established bronchiectasis, careful microbiologic surveillance in the stable and exacerbated states is needed. Clinicians need to be aware of local microbiologic data and need to track the results in individual patients. Close interaction with the local microbiology laboratory may also improve antibiotic stewardship for patients with bronchiectasis. Clinicians should strongly consider establishing a protocol for obtaining sputum cultures at regular intervals in their bronchiectasis patients based upon local infection patterns and overall experience with their patients. It is clear that routine bacterial and mycobacterial surveillance is needed; routine fungal cultures may or may not be of value and viral cultures are probably most worthwhile at times of exacerbation. More research is needed in this area to better standardize the role of microbiology cultures and microbiome results in improving the clinical outcomes of patients with bronchiectasis.

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