Review

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Bacterial infections in patients with primary ciliary dyskinesia: Comparison with cystic fibrosis

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Abstract

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder associated with severely impaired mucociliary clearance caused by defects in ciliary structure and function. Although recurrent bacterial infection of the respiratory tract is one of the major clinical features of this disease, PCD airway microbiology is understudied. Despite the differences in pathophysiology, assumptions about respiratory tract infections in patients with PCD are often extrapolated from cystic fibrosis (CF) airway microbiology. This review aims to summarize the current understanding of bacterial infections in patients with PCD, including infections with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Moraxella catarrhalis*, as it relates to bacterial infections in patients with CF. Further, we will discuss current and potential future treatment strategies aimed at improving the care of patients with PCD suffering from recurring bacterial infections.

Keywords

PCD, CF, microbiology, infections, airways

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Introduction

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder associated with defects in ciliary biogenesis, structure, and function and is characterized by chronic oto-sinopulmonary disease.[1,2] Although first described in 1936,[3] PCD was not attributed to "immotile cilia" and impaired mucociliary clearance until 1976.[4]

One of the clinical features of PCD is persistent or recurring bacterial infection of the sinuses, ears, and airways.[2,5] The microbiology of the PCD airways is understudied, and assumptions about colonization make use of data from cystic fibrosis (CF). However, the pathophysiology of the two diseases is different. In contrast to PCD, CF is caused by a defect in the CF transmembrane conductance regulator (CFTR) protein which leads to the accumulation of thick sticky mucus in the airways. Nonetheless, both diseases are in part characterized by impaired mucociliary clearance. In PCD, the impaired mucociliary clearance is caused by malfunctioning cilia, which fail to propel mucus upward.[1] In CF, there is increased secretion of mucus and decreased airway fluid from the excessive absorption of water by the airway epithelia. The dehydrated, thick mucous layer compresses the cilia, thereby inhibiting their function and severely impairing mucociliary clearance.[6–8]

Indeed, the microbiology of the airways in patients with PCD seems to mirror that of CF

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patients to some extent.[2,9–19] In addition, the bacterial colonization patterns in an individual CF patient's airways change relatively little over time if the patient is clinically stable.[20,21] Similar trends have been reported in patients with PCD.[9] However, there are important differences in airway microbiology between CF and PCD.

Considering the fact that bacterial infections are a principal cause of morbidity and mortality for patients with CF,[22] and are associated with morbidity and mortality for patients with PCD, a thorough understanding of the airway microbiology of both diseases is fundamental to improving patient care. This review aims to summarize the current understanding of bacterial infections in patients with PCD as it compares to bacterial infections in patients with CF.

Pathogens recovered from PCD airways

In contrast to CF, where *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common bacterial pathogens,[10,11,14] *Haemophilus influenzae* is the pathogen most commonly isolated from patients with PCD, at least until adolescence/early adulthood.[2,17,18] *P. aeruginosa* is also common, especially in adult patients,[2,18,19] but mucoid *P. aeruginosa* is not typically isolated from PCD patients until after age 30.[2] Other bacterial species commonly recovered from sputum samples of patients with PCD include *S. aureus*, *Streptococcus pneumoniae*, and nontuberculous Mycobacteria,[2,15,17] and species of the genus *Ralstonia*, *Moraxella catarrhalis*, and *Achromobacter xylosoxidans* have been isolated as well.[9,16,19] Interestingly, *Burkholderia cepacia* complex (Bcc) organisms, some of which are important bacterial pathogens in patients with CF,[23] have to date not been isolated from patients with PCD.

Haemophilus influenzae. *H. influenzae* is a gram-negative coccobacillus that can grow both aerobically and anaerobically.[24] The strains of *H. influenzae* can be subdivided into typeable (polysaccharide capsule present) serotypes (a through f) and nontypeable (polysaccharide capsule absent) numbered biotypes.[24]

H. influenzae is commonly isolated from young children with CF, with an estimated prevalence of 20% in children under the age of 1 year, and of approximately 32% in children with CF between the age of 2 and 5.[11,14] After age 5, however, the prevalence of *H. influenzae* declines with age, and its estimated prevalence in adults with CF between the age 18 and 24 is less than 10%.[11,14] However, the overall percentage of people with CF infected with *H. influenzae* has remained relatively steady (between 15% and 20%) since 1995.[14] The majority of *H. influenzae* strains isolated from CF patients are nontypeable, with biotype 1 being the most prevalent.[10,11,25]

In patients with CF, *H. influenzae* infection most commonly manifests as a chronic lung infection and may be associated with acute exacerbations.[12] Additionally, *H. influenza* is speculated to be a cause of pneumonia in children and adults with CF, although the available evidence is limited.[26] Similar to other bacterial species, the reasons as to why *H. influenzae* has a predilection to infect the CF airway is unknown and is an area of great research interest. Although *H. influenzae* possesses a variety of virulence factors, biofilm formation by this pathogen, in particular, appears to contribute to the establishment of chronic infections in CF airways.[12,26,27]

In patients with PCD, *H. influenzae* persists into adolescence/early adulthood as the organism most commonly isolated from the airways, with one study reporting a prevalence of 80% in children under age 18 and a prevalence of 22% in adults.[2] More recent studies, however, reported a prevalence of 32–65% in children and adolescents,[9–19] and of approximately 21–27% in adults.[18,19] Therefore, data from these studies indicate that the prevalence of *H. influenza* infection in patients with PCD declines with age, comparable to what is observed in CF.[2,18,19]

Interestingly, several studies reported no significant impact of *H. influenzae* infection on lung function, as measured by forced expiratory volume in 1 second (FEV_1), in patients with PCD.[2,9,16,17]

P. aeruginosa (mucoid and nonmucoid). *P. aeruginosa* is a gram-negative, rod-shaped, opportunistic pathogen that is metabolically diverse.[28] Although *P. aeruginosa* prioritizes aerobic respiration, it is well adapted to anaerobic conditions.[29–31] *P. aeruginosa* has been isolated from a variety of environments, including soil, water, hospitals, and human skin.[28–32]

P. aeruginosa has long been recognized as an important pathogen in patients with CF, with an estimated prevalence of approximately 50% in 2014.[14] For patients with CF, acquisition of this pathogen often occurs early in life. In 2014, approximately 20% of patients under age 5 were reported to have been infected with *P. aeruginosa*.[14] In addition, it is estimated that 60–70% of patients with CF are infected by this organism by age 20,[33] and that prevalence

peaks at approximately 75% in patients between the age of 35 and 44.[14] Interestingly, recent data suggest that administration of inhaled antibiotics such as tobramycin, colistin, levofloxacin, or aztreonam may decrease *P. aeruginosa* density in sputum; and in some cases, inhaled antibiotics may eradicate it from the airways of patients with CF in which it has been isolated for the first time or has not been isolated in 2 years or more.[34–39] Moreover, the most recent guidelines from the CF Foundation recommend the administration of inhaled tobramycin (without the addition of oral antibiotics) for 28 days for the eradication of early *P. aeruginosa* infection.[40] Other strategies for the eradication of *P. aeruginosa* infection in patients with CF include the administration of oral antibiotics such as ciprofloxacin, either alone or in combination with inhaled antibiotics,[41] or the administrations of intravenous antibiotics.[42] None of these other strategies have been evaluated in large, randomized clinical trials. Although there is general agreement regarding the use of inhaled antibiotics, particularly 28 days of tobramycin, as the primary management strategy for the eradication of first isolates of *P. aeruginosa*, there is no consensus on the management if this strategy fails to eradicate *P. aeruginosa* or if the *P. aeruginosa* is reisolated on subsequent cultures shortly thereafter. In accordance with these findings, the CF Foundation has reported a decline in the overall prevalence of *P. aeruginosa* infection.[14]

P. aeruginosa produces many virulence factors, including exoenzymes that damage host cells, a flagellum for motility, biofilm formation for protection, lipopolysaccharides for host cell entry, and pili for attachment.[10,28] Furthermore, studies have indicated that the sputum environment inside the CF airways contains hypoxic/anaerobic zones and that *P. aeruginosa* is well adapted to these conditions.[30,31,43,44] Two important aspects that enable this organism to thrive in this environment are biofilm formation and anaerobic respiration/denitrification. These functions depend on a variety of factors, including nitric oxide (NO) reductase to decrease the buildup of toxic NO, the *rhl* quorum sensing system, and the OprF outer membrane protein.[31,44] Further, *P. aeruginosa* colonization affects the nitrogen redox ecology in the CF lungs. Gaston and colleagues showed that sputum from patients with CF who were exclusively colonized with *P. aeruginosa* contained more NH_4^+, a denitrification product, than the sputum from non-CF control patients.[45] In addition, sputum NH_4^+ concentrations decreased after antipseudomonal therapy.[45] Since high NH_4^+ concentrations inhibit chloride transport in the intestinal epithelium,[46] eliminating *P. aeruginosa* may attenuate some of the defects in epithelial chloride transport.[45]

Another important aspect of *P. aeruginosa* infection in patients with CF is (the transition to) the mucoid phenotype, which is characterized by the secretion of large amounts of slimy polysaccharide that surround the bacterial cells.[10] Early in the course of infection, nonmucoid varieties of *P. aeruginosa* predominate.[47,48] The transition to the mucoid phenotype appears to be important for the establishment of chronic *P. aeruginosa* infections in CF airways, and the mucoid phenotype therefore becomes the most common phenotype later in the course of infection.[10,49,50] Further, the conversion to the mucoid phenotype has been associated with an accelerated decline in lung function.[51]

In patients with PCD, *P. aeruginosa* is an important pathogen as well, with a reported prevalence of 20–36% and 5–7% for nonmucoid and mucoid phenotypes, respectively, in children and adolescents.[2,16,17] Further, Chang et al. recently reported a total prevalence of 35% for both *P. aeruginosa* phenotypes in pediatric patients.[18] In adult patients, the overall prevalence of nonmucoid and mucoid *P. aeruginosa* is higher and is estimated to be approximately 27% for each phenotype.[2] Accordingly, the total prevalence of *P. aeruginosa* infection (nonmucoid and mucoid) in adult patients has recently been reported at 51%.[18] Therefore, the prevalence of *P. aeruginosa* appears to increase with age, especially after age 30.[2,9,18,19] Perhaps, after years of progressive bronchiectasis, impaired mucociliary clearance and lung damage, the environment inside the airways of patients with PCD is more suitable for (chronic) *P. aeruginosa* infection.

Interestingly, it has been suggested that the transition to the mucoid phenotype occurs typically much later in patients with PCD, not until after age 30.[2] In patients with CF, the conversion to the mucoid phenotype is often the result of a mutation in the *mucA* gene, transcription of which normally prevents overproduction of alginate.[8,52] This mutation, in turn, may be induced by mutagenic reactive oxygen species produced by neutrophils, such as hydrogen peroxide.[8,53]

In addition, although it is widely recognized that (chronic) infection with *P. aeruginosa* is associated with a decrease in lung function and an increased risk of death in patients with CF,[10,11,51,54] it is unclear to what extent (chronic) *P. aeruginosa* infection contributes to the clinical outcomes of PCD patients. In

2013, Rogers and colleagues reported a negative correlation between the abundance of *Pseudomonas* in PCD airways and lung function.[9] In 2004, Noone and colleagues reported that especially infection with mucoid *P. aeruginosa* may be associated with a decrease in lung function.[2] However, more recently, Maglione and colleagues and Davis and colleagues reported no significant correlations between *P. aeruginosa* infection and lung function.[16,17]

Staphylococcus aureus. *S. aureus* is a gram-positive, facultative anaerobic, coccal bacterium that is a permanent part of the normal flora of the nostrils of approximately 20% of the population and is carried intermittently by approximately 30% of the population.[55] The most concerning strains of *S. aureus* are the methicillin-resistant strains (MRSA). In 2004, the National Nosocomial Infection Surveillance reported that more than 60% of *S. aureus* isolates from US hospital intensive care units represent MRSA.[56]

S. aureus was not only the first organism recognized to cause chronic infections in patients with CF, but it was believed to be the leading cause of mortality in patients with CF early on as well.[10] Currently, *S. aureus* is still one of the pathogens most commonly isolated from patients with CF. More specifically, in 2014, approximately 80% of patients aged 6 to 17 years with CF were reported to be infected by this pathogen.[14] Furthermore, although the prevalence of *S. aureus* infection decreases somewhat as patients reach adulthood, it still remains significant and is estimated to be between 40% and 50%.[14,57]

S. aureus employs a variety of virulence factors to cause disease. Adhesion proteins for attachment to airway epithelial cells, and a wide array of factors involved in host immune evasion, are among the most significant.[10,58] Moreover, MRSA strains possess the *mecA* gene, which codes for penicillin-binding protein 2a (PBP2a). This protein is insensitive to the action of methicillin and thereby confers methicillin resistance to the organism.[59]

Both methicillin-resistant and methicillin-sensitive strains have been associated with a decline in lung function in pediatric and adolescent patients with CF. In 2008, Dasenbrook and colleagues reported that the decline in FEV_1 was 43% more rapid in CF patients (aged 8–21) with a persistent MRSA infection than in uninfected patients.[60] In 2013, Wolter and colleagues reported that pediatric CF patients infected with methicillin-sensitive *S. aureus* experienced a 7.9% decline in FEV_1 compared to a 1.9% decline in uninfected patients.[61] Interestingly, Ren and colleagues reported a stronger decline in lung function in CF patients infected with MRSA in comparison to patients infected with methicillin-sensitive *S. aureus*.[62]

Several studies have not found an association between persistent infection with *S. aureus* to a decline in lung function in patients with PCD.[2,9,16,17] According to recent studies, the approximate prevalence of *S. aureus* infection in pediatric and adolescent patients with PCD is 35–46%.[16,17] Interestingly, at least according to two recent studies, the prevalence of *S. aureus* infection peaks during adolescence.[18,19] However, the prevalence of *S. aureus* tends to decrease as PCD patients reach adulthood and beyond,[2,18,19] with studies reporting a prevalence of 6–20% in adult patients.[2,18,19]

Streptococcus pneumoniae. *S. pneumoniae* is a gram-positive, facultative anaerobic coccus that is usually found in pairs, known as diplococci. Currently, there are 92 known serotypes of this organism, which differ greatly in prevalence and in their ability to cause disease.[63] *S. pneumoniae* is commonly carried in the upper respiratory tract of healthy, young children under age 6, although the exact prevalence varies widely depending on the study population.[64–66] However, it is apparent that the prevalence of *S. pneumoniae* carriage decreases with age.[64,66] In healthy infants and children, the serotypes 3, 19F, 23F, 19A, 6B, and 14 are the ones most commonly carried.[65] One of the most characteristic virulence factors of *S. pneumoniae* is its polysaccharide capsule, which is unique for each serotype and aids in the protection against the host's immune system.[67] Studies indicate that the capsule protects against phagocytosis[68] and that it may influence the amount of antibody that is able to bind to the organism's surface antigens.[69]

For patients with CF, *S. pneumoniae* is primarily considered to be a transient pathogen.[13,70] In children with CF, the prevalence of *S. pneumoniae* infection is approximately between 5% and 20%.[71–73] In adults with CF, the prevalence (approximately 5%) of this pathogen is even lower.[70] In patients with CF, the serotypes 19F, 5, 4, 3, 23F, 6A, 6B, and 9V are most commonly isolated.[71–73]

The contribution of *S. pneumoniae* to lung disease in patients with CF is not clear, in part because *S. pneumoniae* is isolated in association with other bacterial respiratory pathogens approximately 84.1% of the time.[73] In 2005, Del Campo and colleagues reported that 35% of CF patients with *S. pneumoniae*

infection presented with acute exacerbations, but that only 27% of these patients were not colonized by any other common CF pathogen.[71] Recently, Paganin and colleagues reported a significant association between *S. pneumonia* infection and a decline in lung function in patients with CF,[74] but a different group found no such correlation.[70]

S. pneumoniae is commonly isolated from pediatric and adult patients with PCD as well.[9,15,16,18] One study reports that *S. pneumoniae* is the second most commonly isolated pathogen from the airways of pediatric and adolescent patients with PCD after *H. influenzae* with an estimated prevalence of 52%.[17] Davis and colleagues and Chang and colleagues, on the other hand, recently reported a prevalence of 21–30% in pediatric and adolescent patients.[16,18] Further, at least one large, recent study suggests that the prevalence of *S. pneumoniae* infection declines with age.[18] Currently, no significant relationship between *S. pneumoniae* infection and lung function in patients with PCD has been reported.[9,16,17]

Moraxella catarrhalis. *M. catarrhalis* is a nonmotile, gram-negative, aerobic, diplococcal bacterium.[75] Among the general pediatric population, acquisition of this pathogen is quite common, although the prevalence varies widely depending on the population studied.[75] Furthermore, *M. catarrhalis* is one of the most common causes of acute otitis media in children, and it is estimated that 15–20% of the episodes of acute otitis media are caused by this pathogen.[75] In addition, *M. catarrhalis* has been associated with otitis media with effusion,[76] chronic obstructive pulmonary disease,[77] and sinusitis.[78]

M. catarrhalis possesses a wide variety of virulence factors that cause disease in the sinuses, ears, and airways. For example, *M. catarrhalis* biofilms are frequently detected in children with chronic otitis media.[79] Other virulence factors include adhesins for attachment to human epithelial cells,[80–82] and the outer membrane protein OlpA, which serves to protect *M. catarrhalis* from the bactericidal effects of human serum.[83] Resistance to antibiotics is of concern as well, with studies reporting that over 95% of clinical *M. catarrhalis* isolates are resistant to the β-lactamase family of antibiotics.[84,85] Polymicrobial biofilms composed of *M. catarrhalis* and *S. pneumoniae* appear to contribute to antibiotic resistance in patients with otitis media.[86]

Interestingly, *M. catarrhalis* is relatively rarely recovered from the airways of patients with CF,[87–89] with one study reporting a prevalence of 7.40% in pediatric patients between 3 months and 17 years of age.[90]

In patients with PCD, *M. catarrhalis* is regularly isolated from the airways. Davis and colleagues report that *M. catarrhalis* was isolated at least once in 19% of the children included in their study.[16] In addition, Alanin and colleagues reported that 19% of the samples from children younger than 12 years, 9% of the samples from patients between 13 and 25 years of age, and 7% of the samples from adults older than 25 years were positive for *M. catarrhalis*.[19] Therefore, the prevalence of *M. catarrhalis* infection in patients with PCD appears to be decreasing with age.[19] Chang et al. report a similar trend, although their study indicates that the prevalence of *M. catarrhalis* infection spikes during adolescence and then decreases into adulthood.[18] Lastly, Davis et al. reported no association between *M. catarrhalis* infection and lung disease severity in patients with PCD.[16]

A. xylosoxidans and Ralstonia species: Emerging pathogens. *A. xylosoxidans* is an aerobic, gram-negative bacillus that is considered to be an emerging pathogen for patients with CF. The estimated prevalence of *A. xylosoxidans* infection in patients with CF varies widely, ranging anywhere from 3% to 30%.[14,91–94]

Unfortunately, little is known about the pathogenesis and virulence factors of this organism on a molecular level.[91] Some virulence factors, such as a cytotoxin,[95] and biofilm formation,[96] have yet to be characterized. Furthermore, the extent to which *A. xylosoxidans* contributes to CF lung disease is currently unclear, as there are limited data available.[91] At least one study, however, has demonstrated that *A. xylosoxidans* infection may be associated with a more rapid decline in FEV_1.[97] In contrast, De Baets and colleagues found that infected patients with CF tended to have lower FEV_1s at the time of the first positive culture but did not exhibit a more rapid decline in lung function afterward.[98] In addition, Trancassini and colleagues found an increased prevalence of biofilm producing strains of *A. xylosoxidans* in patients with severely impaired lung function.[96] These results, therefore, suggest that patients with more severe lung disease may be predisposed to *A. xylosoxidans* infection. Lastly, as a species capable of denitrification, *A. xylosoxidans* isolated from CF patients has been shown to produce increased nitrous oxide (N_2O) when supplemented with nitrate ion

(NO_3^-).[99] *A. xylosoxidans*, therefore, may affect the nitrogen redox ecology in the CF lungs.

Species from the gram-negative genus *Ralstonia* have been identified as an emerging pathogen in patients with CF over the past decade or so.[100–103] Coenye and colleagues isolated at least 5 different *Ralstonia* species from patients with CF: *R. mannitolilytica*, *R. respiraculi*, *R. pickettii*, *R. basilensis*, and *R. metallidurans*, with *R. mannitolilytica* being the most common, representing 46% of the *Ralstonia* isolates.[101] The exact prevalence of *Ralstonia* infection in patients with CF is unclear, in part because the organism is difficult to isolate but is likely very low.[102] Coenye and colleagues found only 42 *Ralstonia* isolates in 38 patients out of 4000 total specimens.[101,103] In addition, the contribution of *Ralstonia* infections to lung disease in patients with CF is currently unclear.[102]

Both pathogens have also been isolated from the airways of patients with PCD.[9,19] Alanin and colleagues recovered *A. xylosoxidans* from 1% of the samples from children between 0 and 12 years of age, 2% of the samples from patients between 13 and 25, and 6% of the samples from adults older than 25 years, suggesting that *A. xylosoxidans* is more common in adults.[19] Rogers and colleagues detected *Ralstonia* species in 17 out of 24 patients with PCD, of which *R. pickettii* was by far the most common.[9] Rogers and colleagues found no association between lung function and *Ralstonia* infection,[9] and currently no data are available on the contribution of *A xylosoxidans* to lung disease in patients with PCD.

Nontuberculous mycobacteria

Nontuberculous mycobacteria (NTM) are a group of rod-shaped bacilli of the mycobacterial genus of *Actinobacteria* that are specifically not associated with tuberculosis or leprosy. The incidence of NTM infection in the general population is estimated at 1–1.8 in 100,000,[104] but NTM is a far more common cause of disease in susceptible patients such as patients with CF.[11] The prevalence of NTM infection in patients with CF is estimated to be anywhere between 6% and 13%[105] and appears to be increasing.[105,106]

The vast majority of NTM infections in patients with CF in the United States are caused by one of two species complexes: *Mycobacterium avium* complex, which accounts for approximately 72% of the NTM infections, and *Mycobacterium abscessus* complex, which accounts for 16–68% of the NTM infections.[105] Other species, such as *Mycobacterium simiae* and *Mycobacterium kansasii*, have been isolated as well.[11,105] Interestingly, in CF, NTM infection appears to be associated with older age.[105,107–109]

Previously, there was no consensus on the risks and clinical outcomes associated with NTM infections for patients with CF.[105] At least two studies reported that NTM infection had no impact on the progression of disease in patients with CF.[107,110] However, it is becoming more clear that NTM infections present a major threat to the lung health of people with CF. More recent studies have reported that NTM infection may be associated with a decline in FEV_1.[111,112] In addition, the prevalence of NTM is increasing in CF.[14] Further, NTM infection appears to be relatively common in patients with end-stage CF referred for lung transplantation, with one study reporting a prevalence of 19.7%.[113] The NTM may be associated with severe complications in lung transplant recipients and therefore may be considered a contraindication by some centers.[114] Nonetheless, there is evidence that post-transplant NTM infection can be treated successfully and that favorable survival can be achieved.[115]

In order to cause disease, NTM species such as *M. avium* complex species must penetrate the airway epithelium. They appear to do so at damaged sites,[116] and fibronectin attachment proteins appear to play an important role in bacterial attachment and invasion.[117,118] In addition, the cellular envelope appears to be important for NTM intracellular survival.[119] Lastly, it appears as though some NTM species are able to acquire virulence genes from other bacterial CF pathogens such as *P. aeruginosa* and *B. cepacia*.[120]

The NTM is also more commonly isolated from adult than pediatric PCD patients, with one study reporting prevalences of 18% and 0%, respectively.[2] One recent study reported that NTM was isolated from only 3 of 118 pediatric and adolescent patients with PCD.[16] On the other hand, Alanin and colleagues and Chang and colleagues reported that NTM was isolated from only 1 of 107 and 11% of patients (pediatric and adult), respectively.[18,19] Unfortunately, although Noone and colleagues point out that NTM may require an aggressive multidrug treatment regimen.[2] However, much knowledge regarding NTM infections in patients with PCD remains to be further investigated.

B. cepacia *complex species.*

The *B. cepacia* complex (Bcc) is a group of similar species of gram-negative,

metabolically diverse bacilli.[121] Some members of the *B. cepacia* complex are opportunistic pathogens that may cause disease in susceptible patients, such as patients with granulomatous disease[122] and patients with CF.[123]

The Bcc species most commonly isolated from the airways of patients with CF are *B. multivorans*, *B. cenocepacia*, and *B. vietnamiensis*, accounting for approximately 37%, 31%, and 5% of Bcc infections, respectively, between 1997 and 2007.[11] Overall, the prevalence of Bcc infection in patients with CF is relatively low, ranging from less than 3% to approximately 8%, and appears to be higher in adult patients.[11,14,124,125]

Despite their low prevalence, the clinical consequences of Bcc infection may be severe. For example, Bcc infection has been associated with increased morbidity and mortality in patients with CF.[126,127] Although some infected patients will exhibit a gradual decline in lung function,[123] others (approximately 20%)[128] may suffer from fatal "cepacia syndrome," which is characterized by necrotizing pneumonia and sometimes septicemia, and may result in death in less than 1 year.[123,128,129]

Research into the virulence factors of Bcc species, particularly over the last decade, has increased our understanding of how Bcc species cause disease.[130] Notable virulence factors include biofilm formation for protection,[130] flagella for motility and host cell invasion,[131] and RpoE, an alternative sigma factor that allows *B. cenocepacia* to delay phagolysosomal fusion.[132] Another distinctive virulence factor is the cable pilus, which allows for bacterial binding to the epithelium of CF airways.[133] This particular virulence factor is associated with certain strains such as J2315, a multidrug-resistant strain associated with patient-to-patient transmission.[134,135] Furthermore, Bcc species may affect the nitrogen redox ecology in the CF lungs, as Kolpen and colleagues have demonstrated that *B. multivorans*, isolated from CF patients, produced increased N_2O, when supplemented with NO_3^-.[99]

Another intriguing attribute of Bcc species is that they are able to "communicate" with *P. aeruginosa* through quorum sensing. Riedel and colleagues demonstrated that *B. cepacia* is able to utilize *N*-acyl-homoserine lactone (AHL) signals produced by *P. aeruginosa*,[136] and, indeed, Bcc species are able to form mixed biofilms with *P. aeruginosa*.[137,138] Schwab and colleagues even suggest that Bcc species may inhibit the growth of *P. aeruginosa* biofilms.[139]

Interestingly, Bcc species have not been isolated to date from the airways of patients with PCD. Rogers and colleagues, using quantitative polymerase chain reaction (PCR), did not find Bcc isolates from the airways of patients with PCD.[9] Therefore, it remains to be investigated whether Bcc member species are able to infect the airways of patients with PCD, and if not, the reasons should be investigated.

Anaerobic bacteria

Although not routinely screened for in sputum, anaerobic bacterial species have been isolated from the lungs of patients with CF using specific anaerobic culture and culture-independent methods.[140,141] Tunney and colleagues detected anaerobic bacteria in 64% of sputum samples from patients with CF.[142] In addition, Bittar et al., using molecular techniques, reported that 30% of the bacterial species isolated from the sputum of patients with CF were anaerobes.[143] Overall, species from the genera *Prevotella*, *Veillonella*, *Propionibacterium*, and *Actinomyces* are among the anaerobes most commonly isolated from CF airways.[140,144]

The role that anaerobic bacteria play in CF lung disease is unclear. For example, one study indicates that the *Streptococcus milleri* group is associated with pulmonary exacerbations and thereby contributes to CF lung disease.[145] However, Worlitzsch and colleagues reported that after therapy with antibiotics, lung function improved without a reduction in the number of obligate anaerobes.[146] The latter study, therefore, may suggest that anaerobes play little to no role in CF lung disease.[141]

While conventional microbiological practices fail to detect anaerobic bacteria, at least one study has reported the isolation of anaerobic bacteria from the airways of patients with PCD using quantitative PCR.[9] The isolated anaerobes include species from the genera *Prevotella*, *Neisseria*, *Porphyromonas*, *Actinomyces*, and *Veillonella*,[9] some of which have been isolated from the lungs of patients with CF as well.[140,142,144] The anaerobic genus *Provotella* was considered to be dominant in two patients included in their study.[9] Although Rogers et al. did not find any negative correlations between the presence of anaerobic bacteria such as *Provotella* and lung function as determined by FEV_1,[9] the contribution of anaerobic bacteria to lung disease in PCD remains unclear.

Table 1. Summary of airway microbiology in patients with CF and patients with PCD.

	Common in pediatric patients		Common in adult patients		Associated with lung disease/ decline in lung function	
Airway pathogen	PCD	CF	PCD	CF	PCD	CF
Haemophilus influenzae	++[a]	+	+	±	Unclear	Y
Pseudomonas aeruginosa	+	++	++[a]	++[a]	Unclear	Y
Staphylococcus aureus	++/+	++[a]	+/±	++	Unclear	Y
Streptococcus pneumoniae	++/+	±/-	+	–	Unclear	Unclear
Moraxella catarrhalis	+/±	±/-	±/-	–	Unclear	Unclear
Achromobacter xylosoxidans	–	+/±/-	–	+/±/-	Unclear	Unclear
Ralstonia sp.	Unknown	–	Unknown	–	Unclear	Unclear
NTM	–/-	±/-	±/-	±/-	Unclear	Unclear
Burkholderia cepacia complex species	[b]	±/-	[b]	±/-	Unclear	Y
Anaerobes	Unknown	++	Unknown	++	Unclear	Unclear

PCD: primary ciliary dyskinesia; CF: cystic fibrosis; NTM: nontuberculous mycobacteria; sp.: species.
[a]Pathogens *most* commonly isolated from patients with this disease at this stage (pediatric/adult); ++ indicates very common pathogens (prevalence ~50% or greater); + indicates common pathogens (prevalence ~25%); ± indicates relatively common pathogens (prevalence ~10%); - indicates rare pathogens (prevalence ~5%); – indicates very rare pathogens (prevalence ~1% and less).
[b]Pathogen has to date not been isolated from the airways of this patient population.

Current and potential treatment strategies for bacterial infections in PCD

Recently, Shapiro et al. published extensive consensus guidelines on the diagnosis, monitoring, and treatment of PCD, including the treatment of (recurring) bacterial infections.[147] In addition to antibiotics and other treatment options reviewed by Shapiro and colleagues,[147] other strategies to combat bacterial infections in patients with CF and PCD may be available in the future.

One such strategy is bacteriophage therapy. Bacteriophages are viruses that exclusively infect bacteria, and one of the major advantages in utilizing them as a treatment strategy is their high specificity to target bacteria.[148]

Various studies have demonstrated the ability of phages to eliminate common CF pathogens in vitro. Alemayehu and colleagues showed how two phages are able to drastically reduce the amount of *P. aeruginosa* cells growing in a biofilm on CF airway cells.[149] More recently, Saussereau and colleagues demonstrated that a cocktail of 10 bacteriophages is effective at reducing the levels of *P. aeruginosa* in sputum samples from patients with CF.[150] However, there is also substantial evidence demonstrating that *P. aeruginosa* biofilms may develop phage resistance in as little as 24 hours,[151,152] which may limit the clinical utility of phage therapy to treat *P. aeruginosa* infections. Clinical data on the safety or efficacy of phage therapy for patients with CF are scarce and are limited to case reports.[153] Therefore, larger, randomized clinical trials are necessary.[153]

Conclusion and future directions

As demonstrated in this review, there is overlap in types of respiratory infections between patients with CF and PCD (Table 1). *H. influenza*, *P. aeruginosa*, and *S. aureus* are all commonly found in the airways of both patient groups. In addition, there exist similar trends in airway microbiology in both patient groups. For instance, many bacterial species, such as *H. influenza*, *S. pneumoniae*, and *S. aureus*, tend to decrease in prevalence with age, after which *P. aeruginosa* becomes the dominant airway pathogen (Table 1).

These similarities have enabled the extrapolation of information from CF airway microbiology to PCD airway microbiology. However, likely in part due to the differences in pathophysiology and underlying etiology, the airway microbiology in patients with PCD is unique and significantly different from the airway microbiology in patients with CF. Although *S. aureus* is the most common pathogen during childhood for patients with CF, *H. influenza* and *S. pneumoniae* appear to be the most common pathogens during early childhood in patients with PCD (Table 1). In addition, although many pathogens tend to decrease in prevalence with age in patients with PCD, this decrease appears to occur at a slower rate than in patients with CF.

Because of the observed differences in airway microbiology between patients with CF and patients with PCD (Table 1), it is important that bacterial infections in patients with PCD be further investigated both on a clinical and a basic science level. A PCD patient registry database, like the one managed by the CF Foundation for patients with CF, may facilitate such microbiological research in PCD.

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