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Epidemiology of infection and current guidelines for infection prevention in cystic fibrosis patients

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SUMMARY

The spectrum of bacterial pathogens encountered in cystic fibrosis (CF) lung disease has expanded over the last decade. In addition to established pathogens, such as *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex and *Staphylococcus aureus*, novel Gram-negative non-fermenter bacteria and non-tuberculous mycobacteria have gained in clinical significance. Air sampling performed in inpatient and outpatient clinics, and analysis of cough aerosols expelled by CF patients provides evidence for potential airborne transmission of CF pathogens. Two outbreaks of '*Mycobacterium abscessus* subsp. *massiliense*' have been reported among CF patients, raising the question of airborne transmission of non-tuberculous mycobacteria. In response to newer epidemiological evidence, international infection control guidance documents have changed. Guideline documents agree on the importance of specifications for ventilation when planning new CF inpatient facilities. New CF units should consider providing negative-pressure inpatient and outpatient rooms to diminish the risk of airborne contamination of ward corridors and communal areas. Air exchange rates of inpatient rooms and pulmonary function testing rooms need to be considered and optimized whenever possible. International guidelines disagree as to whether patients should be requested to wear masks in the hospital environment.

Microbial pathogens of the cystic fibrosis lung

Respiratory infections are the principal cause of morbidity and mortality in cystic fibrosis (CF)-associated disease. The microbiology of CF lung disease has changed substantially in recent decades.[1] This review focuses on changes in the epidemiology of CF pathogens which affect infection control measures. Their impact on the clinical significance for CF lung disease and antimicrobial management strategies is not discussed here.

Historically, a small number of bacterial pathogens such as *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Staphylococcus aureus*, and *Haemophilus influenzae* have been associated with pulmonary infections in CF patients (Figure 1).

In the UK, the frequency of chronic *P. aeruginosa* infection decreased in all age groups between 2008 and 2013. The chronic *P. aeruginosa* carriage rate in adults was 51.1% in 2013.[2] In an analysis undertaken by the Royal Brompton Hospital in London, the number of patients infected with bacteria of the *B. cepacia* complex decreased significantly from 9% in 1990 to 4% in 2005, whereas the incidence of *Stenotrophomonas maltophilia* increased from 1% in 1985 to 4% in 2005.[3] In the USA the prevalence of *P. aeruginosa* and *B. cepacia* complex decreased between 1988 and 2012, whereas the number of patients infected with *S. aureus*, meticillin-resistant *S. aureus* (MRSA) and *S. maltophilia* increased.[4]

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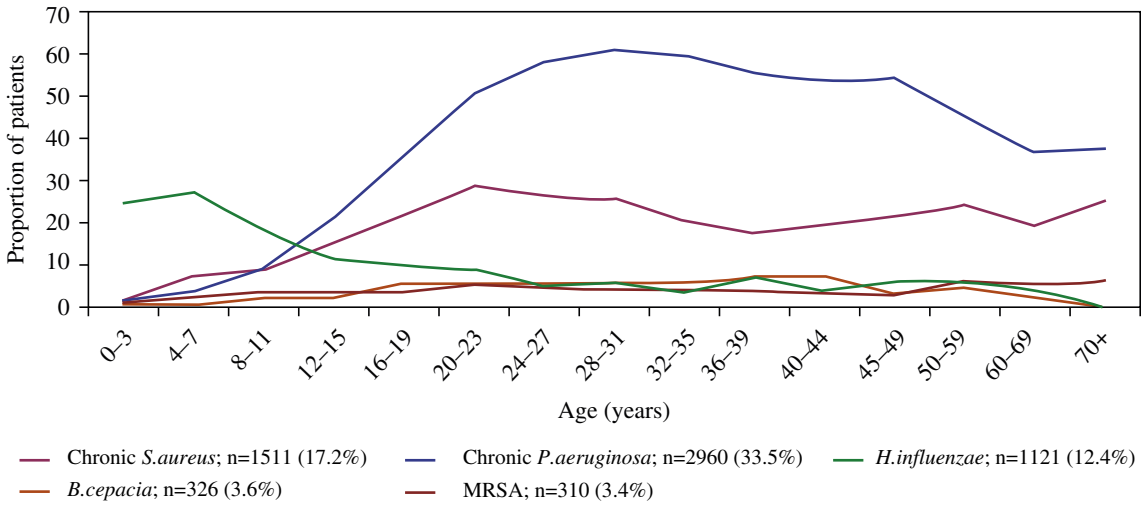

Figure 1. Prevalence of cystic fibrosis bacterial pathogens by age. Reproduced with permission from UK Cystic Fibrosis Registry *Annual data report 2013*, p. 24.[2]

The spectrum of pathogens isolated from CF lungs has grown over the last decade to include novel Gram-negative bacteria, atypical mycobacteria, and a wide range of fungal and viral pathogens. Improved care of CF patients has significantly increased life expectancy to more than 50 years for a baby born in the UK today.[5] Increasing age and multiple, often prolonged, antibiotic treatment courses allow colonization of the CF lung with a wider variety of bacterial and fungal pathogens. Modern molecular identification techniques and the introduction of matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) into laboratory diagnostics have improved identification of bacterial pathogens. Several new species of non-fermenting Gram-negative bacteria, among these *Achromobacter* spp., *Pandoraea* spp., *Ralstonia* spp. and *Inquilinus limosus*, have been associated with CF lung disease.[1] The *B. cepacia* complex family has expanded and currently includes 18 species.[1,6] *Burkholderia gladioli*, although not belonging to the *B. cepacia* complex family, has been described as an important pathogen in CF lung disease.[1] These pathogens are generally isolated from respiratory specimens of adult CF patients and are usually multidrug resistant.

The prevalence of non-tuberculous mycobacteria is increasing among patients with CF.[1] In the USA, *Mycobacterium avium* complex is the most frequently isolated mycobacterium, whereas in Europe *Mycobacterium abscessus* predominates. The overall carriage rate for non-tuberculous mycobacteria in adult CF patients was 7.8% in 2013 in the UK.[2] New whole-genome sequence analysis supports the classification of *M. abscessus* as three subspecies: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii*, and '*M. abscessus* subsp. *massiliense*'.[7–9] The high level of antibiotic resistance among *M. abscessus* and significant adverse effects of current treatment strategies make treatment of *M. abscessus* lung disease challenging.

As with bacterial pathogens, molecular diagnostic techniques have expanded the list of fungal and viral pathogens associated with CF airway disease, but these are not discussed in more detail in this article. In addition to culturable bacteria, modern sequencing techniques have revealed a vast number of bacterial species that are present in the CF lung, the CF microbiome, not culturable by current laboratory methods. Several species of anaerobic bacteria, among these *Prevotella* and *Veillonella* species, have been detected in CF respiratory specimens in quantities comparable to those of *P. aeruginosa*.[10] Representatives of the *Streptococcus milleri* group were found in significant amounts by culture and non-culture techniques in several patients presenting with exacerbations.[11] The clinical significance of anaerobic bacteria and of *S. milleri* for the pathology of CF lung disease needs to be further investigated.[12]

Transmissibility of CF pathogens

Although the majority of CF pathogens are acquired from the environment, there is abundant evidence of patient-to-patient transmission within and outside hospitals. In the 1970s, CF physicians warned that hospitalization is associated with the risk of cross-infection with mucoid *P. aeruginosa*.[13] Since then, outbreaks of transmissible, multidrug-resistant *P. aeruginosa* strains have been reported from CF centres around the world.[14–16] Transmissible *P. aeruginosa* strains are frequently multidrug-resistant and associated with a worse clinical outcome.[17] In the 1990s, evidence accumulated on patient-to-patient transmission of *B. cepacia* complex bacteria.[18] Transmissibility has been documented not only for *B. cenocepacia* strains, but also for other *B. cepacia* strains.[18,19] Similar to established CF pathogens such as *P. aeruginosa* and *B. cepacia* complex, newer Gram-negative non-fermenting pathogens can be transmitted from patient to patient. Two CF patients became infected with *Achromobacter ruhlandii* after indirect contact with a CF patient carrying the same strain.[20] In 2003 Jorgensen *et al.* reported likely cross-infection with *Pandoraea apista* among five CF patients attending a winter camp.[21]

The classic modes of transmission for CF pathogens are direct or indirect exposure to respiratory secretions and droplet transmission. Droplets are larger particles with a size of $\geq$5 μm and are unable to stay airborne for prolonged periods. Droplets were previously estimated to settle within 1 m, although, depending on environmental circumstances, they could travel up to 3 m.[22] By contrast, droplet nuclei are of smaller size ($\leq$5 μm), can travel further, and stay airborne for

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