

MICROBIOLOGY TOPIC:



New and Emerging Respiratory Tract Infections in People with Cystic Fibrosis

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INTRODUCTION

In cystic fibrosis, mutations in the CFTR gene lead to biochemical alterations in the respiratory tract, which, in some way, seem to predispose the lungs to bacterial infections.

This article addresses four questions:

- (i) What unusual bacteria can be found in the lungs of people with CF,
- (ii) What is the prevalence and the clinical relevance of these organisms,
- (iii) What is the potential impact of these organisms on the CF community, and
- (iv) How will these bacteria affect future maintenance and treatment of CF patients?

Respiratory Tract Infections in CF

Airway infections in people with CF (PWCF) are characterized by intercurrent acute exacerbations with fever, weight loss, increased cough, change in volume, colour or appearance of sputum, increased respiratory rate and appearance of infiltrates on chest radiographs. Typically, periods of relative well-being are followed by episodes of these pulmonary exacerbations, which result in progressive deterioration in lung function. Although the median survival age of CF patients has doubled from 14 to 28 years between 1969 and 1990 (largely because of improvement of antimicrobial therapy), chronic pulmonary infection is still one of the most important causes of death.

Common bacterial pathogens in young children with CF are *Staphylococcus aureus* and *Haemophilus influenzae*. During adolescence *Pseudomonas aeruginosa* infection becomes common. The overall *P. aeruginosa* colonization rate in US CF patients is approximately 60%, ranging from approximately 20% in children younger than 1 year to more than 80% in patients aged 26 years or older.

Novel Bacteria

1. The *Burkholderia cepacia* Complex

“...‘*cepacia* syndrome’ is characterised by pneumonia and sepsis...”

Burkholderia cepacia is originally known as the causative agent of soft-rot on onions (see Figure 1). The first reports of infection of CF patients with *B. cepacia* appeared in the late 1970s and early 1980s. In 1984 the increasing prevalence of *B. cepacia* infection among patients receiving care in the Toronto CF center (Canada) and the occurrence in some patients of a rapidly progressing deterioration in respiratory function was described. This so-called ‘*cepacia* syndrome’ is characterised by pneumonia and sepsis, and was observed in as many as 20% of infected patients. Similar increases of respiratory tract infection with *B. cepacia* were subsequently noted in other CF treatment centers in North-America and Europe.

Initial studies (performed from the early 1990s on) showed that there was a remarkable diversity among presumed *B. cepacia* isolates. During the past few years, several taxonomic studies (taxonomy is the field in biology which aims to classify all living organisms into groups on the basis of similarity) have indicated that strains (specific ‘individuals’ within the total population of a bacterial species) initially identified as *B. cepacia* actually represent a complex of several closely related species. This group, collectively referred to as the *B. cepacia* complex, currently consists of nine species. Some of those species were given their own species name, while others are still waiting for a new formal name and are currently designated as *B. cepacia* ‘genomovars’ (see Table).

Table: Distribution of species among *B. cepacia* complex isolates recovered from people with CF in the USA, Canada and Italy (in %)

	New formal name	US	Canada	Italy
Gv I		2.6	0.2	4.1
Gv II	<i>Burkholderia multivorans</i>	37.8	9.3	5.4
Gv III		50.0	80.0	86.5
Gv IV	<i>Burkholderia stabilis</i>	0.2	3.8	4.1
Gv V	<i>Burkholderia vietnamiensis</i>	5.1	1.6	-
Gv VI		2.0	-	-
Gv VII	<i>Burkholderia ambifaria</i>	0.7	-	-
Other		1.6	1.8	-

Clustering of new cases in some centers and the decrease of colonisation of new patients following segregation of colonised and non-colonised patients in other centers suggested

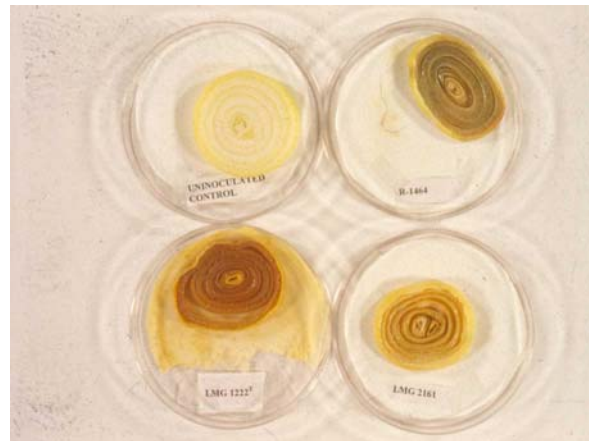
that *B. cepacia* complex strains could be transmitted between CF patients; subsequent studies (employing state-of-the art molecular epidemiological tools) showed that *B. cepacia* complex strains can spread between CF patients via simultaneous hospital admissions or social contact. As a result of these findings new guidelines were issued to reduce the risk of *B. cepacia* complex acquisition. These included discontinued sponsorship and support of CF summer camps and segregation of colonised patients.

“...infection control measures have a tremendous impact on the life of PWCF...”

These infection control measures have a tremendous impact on the life of PWCF and are not accepted by all CF patients and care-givers. Recent observations (including the observation that strict infection control measures have reduced but not eliminated new infections) have suggested that novel *B. cepacia* complex strains can be acquired from the environment; subsequently, several studies have showed that *B. cepacia* complex can indeed be recovered from some agricultural soils.

Figure 1:

B. cepacia isolates infecting onions.



All nine species belonging to the *B. cepacia* complex have been identified in CF sputum cultures, but the distribution of these species among CF patients is quite disproportionate (see Table). It is clear that *B. cepacia* genomovars III and II (renamed *Burkholderia multivorans*) are most frequently recovered from infected CF patients worldwide. From molecular epidemiologic studies, it is also clear that a few specific strains (e.g. the ET12 clone and the PHDC clone) of *B. cepacia* genomovar III have been identified as infecting large numbers of patients. Whether or not this indicates that *B. cepacia* genomovar III (or specific strains of *B. cepacia* genomovar III) are *per se* more virulent is at present unclear since rigorous comparisons of clinical outcome between persons infected with different *B. cepacia* complex species or specific strains have not yet been undertaken. At present, the data only suggest an enhanced capacity for human infection by specific strains of *B. cepacia* genomovar III, for which the biological basis is at present still unknown.

2. Other *Burkholderia* Species

Burkholderia gladioli is a well-known plant-pathogen, which is traditionally isolated from gladioles and rice. However, CF patients seem to be especially prone to infections with this organism. Nevertheless, compared to *B. cepacia*, the prevalence of *B. gladioli* infection in the CF population is quite low.

Occasionally, other *Burkholderia* species can be found in CF patients as well. These include *Burkholderia pseudomallei* (the causative agent of the tropical disease melioidosis) and *Burkholderia fungorum* (a soil bacterium which is occasionally found in human clinical samples as well). *B. pseudomallei* infections in CF patients appear to be mostly travel-associated, since infections with this organism are usually associated with travel to Southeast-Asia, an area where *B. pseudomallei* is frequently found.

3. *Ralstonia* and *Pandoraea* Species

Bacteria belonging to the genera *Ralstonia* (in particular *Ralstonia pickettii* and *Ralstonia mannitolilytica*) and *Pandoraea* (in particular *P. apista*) can also be found in CF patients. Their occurrence and clinical role have not been systematically investigated and initial data seem to suggest that their prevalence is, at present, rather low (e.g. 1.1% of all Canadian CF patients is colonised with *Ralstonia pickettii*; an equal percentage is colonised by species belonging to the genus *Pandoraea*).

Figure 2: A *Pandoraea* isolate growing on an agar-based medium containing antibiotics and specific dyes.



4. *Achromobacter xylosoxidans* (previously known as *Alcaligenes xylosoxidans*) is an opportunistic human pathogen, capable of causing a wide variety of infections. *A. xylosoxidans* is also capable of causing persistent infection of the respiratory tract of persons with CF, but its precise role in pulmonary decline is not clear. This species is quite prevalent in CF (it infects approximately 9% of all patients in the US). At present there is little evidence that this organism is acquired by patient-to-patient cross-infection.

5. *Stenotrophomonas maltophilia* is increasingly being recognised as an important cause of hospital-acquired infections in debilitated and immunosuppressed individuals and this organism is also resistant to many currently available antimicrobial agents. This organism

was first isolated from CF patients in the mid 1970s and its prevalence has been rising since then. There are large regional differences in prevalence of this organism, with prevalence in North-America (1.8 –10.3%) being lower than in most European countries (up to 25%). Duration of hospitalisation, mechanical ventilation, the use of nebulisers and the amount of antibiotics received seem to be important risk factors for acquisition of *S. maltophilia*. Until now, there are very few reports documenting patient-to-patient spread and since this organism is widespread in the environment, environmental acquisition seems likely. The exact role of this bacterium in respiratory disease is unclear as different studies have shown different clinical outcomes.

6. Enteric bacilli

Members of the bacterial family of the *Enterobacteriaceae* (e.g. *Escherichia coli*, *Klebsiella pneumoniae* and *Serratia marcescens*) can occasionally be found in the lungs of PWCF as well. They are usually transient colonisers and are in general not associated with severe disease.

7. Mycobacteria

“...increasingly being recovered from the respiratory tract...”

Nontuberculous mycobacteria are increasingly being recovered from the respiratory tract of PWCF. The most prevalent species are *Mycobacterium chelonae*, *Mycobacterium abscessus* and *Mycobacterium fortuitum*, although other species have been found as well. Nevertheless, non-tuberculous mycobacteria infections in CF are still rare. In addition, studies have shown that their clinical impact appears to be minimal. It should however be noted that the recovery of these slow-growing organisms is not straightforward as they are often overgrown by other organisms present in CF sputum – hence, their prevalence and clinical impact may have been underestimated.

Occasionally, *Mycobacterium tuberculosis* (the causative agent of tuberculosis) is recovered from the sputum of CF patients as well. It remains to be determined whether people with CF are more susceptible to tuberculosis than people without CF.

8. Other Organisms

Various recent studies have identified a wide range of additional bacteria that can colonise the respiratory tract of PWCF. These include *Inquilinus limosus*, various *Acinetobacter* species, *Bordetella hinzii*, *Comamonas testosteroni*, *Moraxella osloensis* and others. Most of these organisms are only found occasionally and are generally considered to be not dangerous for healthy human beings. The clinical role of these and other unusual (as yet not identified) bacteria in CF lung disease is unclear, although it

seems that at least some of these organisms are capable of prolonged colonisation or spread among CF patients.

PRACTICAL IMPLICATIONS

The finding of these rather unusual bacteria in the lungs of PWCF shows that there is still much to learn about the respiratory micro flora in these patients. The data presented in several recent studies suggest that the CF lung seems to be an ecological niche suitable for the growth of a wide variety of bacteria not commonly associated with human disease. Factors that account for the association between typically non-pathogenic species and the respiratory tract of CF patients are unknown, but the elucidation of these factors may provide important insights into the pathophysiology of CF infection. This would be an important first step towards the development of effective therapies.

“...misidentification as *B. cepacia* complex can have a significant medical, social, and psychological impact ...”

Another important issue is that the majority of the above-mentioned bacteria pose a challenge to clinical microbiology laboratories. Most of these bacteria have only recently been described and they can either not be identified by the lab or are often misidentified as *B. cepacia* complex. This misidentification as *B. cepacia* complex can have a significant medical, social, and psychological impact and should therefore be avoided at all cost. Accurate identification of these unusual organisms is also important to identify outbreaks or to assess their clinical impact.

Recently, a lot of work has been done to improve the existing methodologies and to ‘invent’ new approaches to avoid these misidentifications. These include the use of state-of-the-art molecular-biological tools, including the polymerase chain reaction (PCR). However, these novel methods are not (yet) available in all clinical microbiology laboratories; therefore unusual isolates recovered from CF specimens should be sent to reference laboratories capable of providing more in-depth analyses of these isolates. Examples of these laboratories include:

- (i) the CFF *Burkholderia cepacia* Research Laboratory and Repository at the University of Michigan, Ann Arbor, MI, USA;
- (ii) the *B. cepacia* complex Research and Referral Repository for Canadian CF Clinics at the University of British Columbia, Vancouver, BC, Canada and
- (iii) the Edinburgh Cystic Fibrosis Microbiology Laboratory and Repository at the University of Edinburgh, Scotland, UK.

It should be noted that several other laboratories also provide services for the identification of CF isolates. More information can be obtained from the national CF charitable organisations.

Although systematic studies regarding antimicrobial resistance have only been performed for members of the *B. cepacia* complex and for *S. maltophilia*, it is obvious from anecdotal data that at least some strains of most of the above-mentioned organisms are highly resistant to various antibiotics. Since the resistance patterns of the different strains and species may vary, susceptibility testing can be useful in designing treatment strategies. The combined use of multiple antibiotics may show increased activity; therefore it is useful to test multiple antibiotic combinations ('synergy testing'). To aid in susceptibility testing and synergy studies on multiply resistant organisms isolated from CF patients, the CF Referral Center for Susceptibility and Synergy Studies of Resistant Organisms (Columbia University, New York, NY, USA) was established.

Eradication of *B. cepacia* complex organisms from the lower respiratory tract appears to be virtually impossible, but antibiotic therapy can lead to decreased bacterial density and decreased bacterial virulence production, and hence to a decrease in inflammation and clinical improvement. Examples of antimicrobial combinations that have been shown to show synergy include ciprofloxacin/piperacillin, tobramycine/piperacillin and trimethoprim/ceftazidime. Most *S. maltophilia* strains appear to be susceptible to trimethoprim-sulfamethoxazole (alone or in combination with ticarcillin-clavulanate or a broad spectrum cephalosporin). In addition, new quinolone antibiotics (like sparfloxacin) may be useful for the treatment of *S. maltophilia* infections as well.

It is at present unclear what the impact of these organisms will be on lung transplantation practices. Many treatment centers consider *B. cepacia* complex infection an absolute contraindication to lung transplantation, but as stated higher, additional studies will be required to better define the relative risks associated with each species of the *B. cepacia* complex. At present, no data are available on the outcome of lung transplantations involving patients colonised with any of the other organisms discussed above.

CONCLUDING REMARKS

"...there is still a lot to learn..."

It should be clear that there is still a lot to learn about respiratory tract infections in people with CF. Nevertheless, it should also be clear that significant progress has been made over the last 15 years. It can be expected that these advances in our understanding of the biodiversity of agents responsible for respiratory infections will eventually lead to an improvement of the quality of life of people with CF.

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Editor's Note: For a list of further reading, please contact us: editor@cfww.org