

# Transmissibility and infection control implications of *Burkholderia cepacia* in cystic fibrosis

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**OBJECTIVE:** To describe the microbiology and potential virulence factors of *Burkholderia cepacia*; to discuss the studies that have investigated its mode of transmission among cystic fibrosis patients; and to identify the major risk factors associated with acquisition of this pathogen inside and outside of the hospital environment.

**DATA SOURCES:** MEDLINE search of the literature published between 1986 and 1997 using the key words/subject words *Pseudomonas cepacia*, *Burkholderia cepacia*, cystic fibrosis, infection control and transmissibility, and the bibliography of selected papers.

**DATA EXTRACTION:** Selected studies examining epidemiology, microbiology, virulence factors and mode of transmission of *B cepacia* in cystic fibrosis.

**DATA SYNTHESIS AND CONCLUSIONS:** *B cepacia* is a multidrug-resistant Gram-negative bacillus that has recently been recognized as a major respiratory pathogen in patients with cystic fibrosis. Colonization by this organism can lead to rapid pulmonary deterioration and premature death. Recent studies based on genomic subtyping techniques have suggested that it can be transmitted from person to person. Close social contact and hospitalization have been identified as risk factors for cross-infection. With the implementation of strict infection control policies such as segregation according to colonization status, the rate of new colonization has substantially decreased in most cystic fibrosis treatment centres.

**Key Words:** *Burkholderia cepacia*, *Cystic fibrosis*, *Infection control*, *Pseudomonas cepacia*, *Pulmonary infection*, *Transmissibility*

## Transmissibilité et implications du contrôle de l'infection à *Burkholderia cepacia* dans la fibrose kystique

**OBJECTIF :** Décrire la microbiologie et les facteurs potentiels de virulence de *Burkholderia cepacia* ; examiner les études portant sur son mode de transmission parmi les patients atteints de fibrose kystique ; et identifier les facteurs de risque majeur associés à une contamination par ce pathogène en milieu hospitalier ou extrahospitalier.

**SOURCES DES DONNÉES :** Recherche dans *Medline* des articles publiés entre 1986 et 1997 en utilisant les mots clés/mots sujets *Pseudomonas cepacia*, *Burkholderia cepacia*, fibrose kystique, contrôle de l'infection et transmissibilité, et la bibliographie d'articles choisis.

**EXTRACTION DES DONNÉES :** Études choisies examinant l'épidémiologie, la microbiologie, les facteurs de virulence et le mode de transmission de *B cepacia* dans la fibrose kystique.

**SYNTHÈSE DES DONNÉES ET CONCLUSIONS :** *B cepacia* est un bacille Gram négatif résistant à l'action de plusieurs médicaments et que l'on a récemment identifié comme un des plus importants pathogènes respiratoires chez les patients

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atteints de fibrose kystique. Une colonisation attribuable à cet organisme peut entraîner une détérioration rapide de la fonction respiratoire et une mort prématurée. Des études récentes basées sur des techniques de sous-typage génomique laissent croire que ce bacille peut se transmettre de personne à personne. L'entourage du malade et l'hospitalisation représentent des facteurs de risque pour une infection croisée. Avec la mise en place de mesures strictes de contrôle des infections telles que la ségrégation selon l'état de colonisation, le taux des nouvelles colonisations a diminué de façon appréciable dans la plupart des centres de traitement de la fibrose kystique.

Cystic fibrosis (CF) is the most common lethal genetic disease affecting Caucasians (1). The most frequent mutation that gives rise to this autosomal recessive condition involves the deletion of a phenylalanine residue at position 508 of the gene encoding the CFTR protein, a transmembrane chloride ion transporter in ductal epithelial cells (1). This mutation leads to abnormal chloride secretion or reabsorption in the lung, pancreas and sweat glands. Clinically, CF is characterized by pancreatic enzyme insufficiency and lung disease. Azoospermia is also a common feature seen in more than 95% of young males with CF. However, the major source of mortality in this disease is progressive obstructive lung disease complicated by recurrent respiratory tract infection (1). Insufficient clearance of viscous and mucoid respiratory secretions predisposes CF patients to bacterial colonization, microbial invasion and an inflammatory response at the level of the bronchioles. Common respiratory tract pathogens in CF patients include *Pseudomonas aeruginosa*, *Burkholderia cepacia* (formerly *Pseudomonas cepacia*), *Staphylococcus aureus*, *Haemophilus influenzae*, *Aspergillus fumigatus* and influenza virus. *B cepacia* has recently been recognized as a major pathogen almost exclusively in people with cystic fibrosis (2,3).

### METHODOLOGY

A MEDLINE search was performed for relevant articles published from 1986 to 1997 that examine the epidemiology, microbiology, virulence determinants and the mode of transmission of *B cepacia*. Specific MeSH terms used included "Pseudomonas cepacia", "Burkholderia cepacia", "cystic fibrosis", "respiratory infections", "virulence factors" and "transmissibility". The reference lists of various articles were reviewed for additional relevant publications. This review also includes a discussion of some preliminary molecular epidemiological data investigating the mode of transmission of this organism at the Wellesley Central Hospital Adult Cystic Fibrosis Clinic in Toronto. This review is largely limited to transmissibility and infection control issues related to *B cepacia* colonization and infection in patients with cystic fibrosis only, and does not address disease in other immunocompromised hosts such as those with chronic granulomatous disease.

### MICROBIOLOGY AND VIRULENCE FACTORS

*B cepacia* was originally isolated by Burkholder in 1958 from onions, in which it is known to cause soft rot, but it can also be found in soil, water and occasionally in medical disinfectant solutions (2). It is an aerobic, motile Gram-negative bacillus that is naturally resistant to many antimicrobial agents including ceftazidime and tobramycin. For this reason, infections with the organism are particularly difficult to treat.

*B cepacia* is cultured optimally on selective media, such as MacConkey agar supplemented with polymyxin B, incubated in air at 35°C and requires about 48 h to produce visible colonies. Additional characteristics include the inability to ferment lactose and a weakly positive oxidase reaction. Identification to the species level is often problematic and requires the use of special biochemical and fluorescent enzyme assays (5). In fact, a multicentre study revealed that fewer than one-third of labs surveyed were able to identify the organism correctly (6). Recently, a genetic marker known as 'B cepacia epidemic strain marker' or BCESM has been identified (7). It was found to be conserved among seven different epidemic strains, but only rarely or not at all among environmental and nonepidemic strains, respectively.

Little is known about the virulence factors of *B cepacia*. Although many potential virulence factors are being investigated, their specific roles in pathogenesis remain unclear. It is speculated that the organism successfully colonizes the lungs through adhesins that attach to respiratory epithelium. Recent work done by Goldstein et al (8) at The Hospital for Sick Children, Toronto, Ontario has shown that highly infectious epidemic strains produce long cable-like appendages known as cable pili, which bind tracheobronchial mucin in CF patients. Co-expression of a second type of appendage known as mesh pili is also found in epidemic strains. Mesh pili may facilitate adherence to cells and possibly damage the mucociliary transport system causing inadequate clearance of airway secretions. *B cepacia* may also be able to resist nonoxidative killing by neutrophils (9). In addition, production of elastase and collagenase mediates deeper invasion of the lungs and metastases to the bloodstream (the fulminant cepacia syndrome) (2). The organism has also been shown to invade respiratory epithelial cells and replicate intracellularly (10). This may account for persistent colonization and failure of antibiotic treatment with drugs that are active extracellularly. Other potential virulence factors include exoenzymes, such as lipase, lecithinase and hemolysin, and proteases that can degrade secretory immunoglobulin (2). Furthermore, this species demonstrates multidrug resistance owing to the production of a Bush Group 4 beta-lactamase, a penicillinase not inhibited by clavulanic acid (11), and inherent low outer membrane permeability to aminoglycosides. Co-colonization and/or previous lung infections with *P aeruginosa* probably renders the respiratory tract more susceptible to damage by *B cepacia* (2).

### PREVALENCE AND COLONIZATION

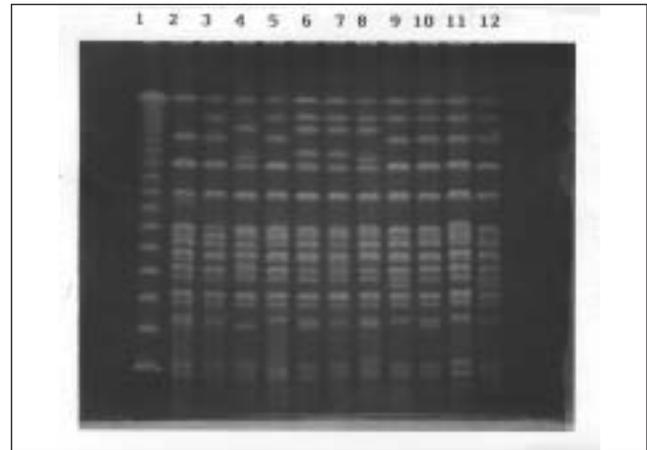
The prevalence of *B cepacia* among CF patients in North America varies between treatment centres and has been reported to be as high as 45% at one paediatric centre (4). Un-

published data from the Canadian and American Cystic Fibrosis Foundations data registries estimate the prevalence in paediatric and adult CF centres in Canada and the United States to be 14% and 3.5%, respectively. Currently, at the Wellesley Central Hospital Adult Cystic Fibrosis Clinic in Toronto, 44% of CF patients are colonized. Those who are infected generally progress along three different clinical pathways. Some individuals simply harbour the organism in the respiratory tract without showing any signs of respiratory deterioration. Others, however, may show a slow but progressive decline in respiratory function. Finally, some experience a rapid decline in respiratory function and premature death. Taylor et al (12) reported that the severity of lung disease at the time of *B cepacia* acquisition was significantly associated with rapid deterioration. Those with severe pulmonary disease (forced expiratory volume in 1 s less than 40% predicted) showed steady or rapid decline in respiratory function, whereas those with mild disease according to pulmonary function tests were stable at the end of the study. In addition, a poor outcome could be expected if the strain acquired was multiresistant (resistant to three or more broad spectrum antibiotics) due to unsuccessful eradication of the organism.

Nonetheless, it remains difficult to predict clinical outcomes based on risk factors alone. Lung transplantation is the only option for those who deteriorate rapidly. However, the Toronto Lung Transplant Group found that double lung transplants were complicated by recolonization with *B cepacia*; the facial sinuses were suspected as the reservoirs for the organism (13). Their overall one-year survival rate was 70%, with the majority of deaths being attributed to pneumonia and septicemia with *B cepacia*. Poor survival rates following transplantation for patients chronically infected with the organism have led many treatment centres to exclude these patients from this option. Studies are currently being conducted to identify host-specific and pathogen-specific factors associated with favourable and lethal outcomes.

### TRANSMISSIBILITY

Much controversy continues to surround the issue of transmissibility of *B cepacia* (14). Can it be transmitted from person to person or is it acquired from environmental sources? Investigations into the mode of transmission have relied on molecular subtyping techniques such as ribotyping and pulsed field gel electrophoresis (PFGE) which has been shown to be more reproducible and discriminatory (15). PFGE involves isolating genomic DNA, cutting it with restriction endonucleases and comparing banding patterns on a gel. If the enzyme chosen provides suitable clarity and separation of bands, and only one or two predominant strain patterns are isolated from a group of epidemiologically linked patients, then person-to-person transmission is considered more likely. On the other hand, if many distinct strains are isolated, then environmental acquisition is suspected. Conflicting reports continue to be published with some groups claiming colonization by one major strain (16-18), while others find no genetic similarity between strains (19). For example, Mahenthiralingam and colleagues (18) in British Columbia recently subtyped over



**Figure 1)** Genomic profiles of 11 randomly selected clinical isolates of *Burkholderia cepacia* from patients attending the Wellesley Central Hospital Adult Cystic Fibrosis Clinic. Lane 1 is a PFGE molecular marker. Lanes 2 to 12 represent patient isolates. These isolates represent a predominant strain pattern among clinic patients

600 isolates of *B cepacia* using a polymerase chain reaction (PCR)-based randomly amplified polymorphic DNA method and found that most patients at each treatment centre studied were colonized by the same strain. On the other hand, Steinbach et al (19) found no relationship between 65 isolates at one centre studied using ribotyping and pulse field gel electrophoresis (PFGE), and thus discounted the importance of person-to-person transmission. The risk of transmission may be strain-dependent with certain strains being more transmissible than others, and this consideration deserves further study.

Preliminary results from a study at the Wellesley Central Hospital Adult Cystic Fibrosis Clinic are also consistent with person-to-person transmission and centre-specific strain predominance. PFGE was used to subtype 127 clinical isolates from different patients following restriction with *Spe1*. Banding patterns were analyzed visually and evaluated according to the Goering criteria (20). Strains were grouped together if their banding patterns were indistinguishable or differed by three bands or less. On the other hand, if they differed by more than three bands, they were considered distinct. According to these criteria, the isolates were classified into two major (type A 40%; type B 52%) and seven minor groups (types C to I 8%). Over 90% of isolates belong to one of the two major strains. These two major strains appear to be closely related, differing on average by four bands and are possibly derived from the same clone. These results were confirmed by randomly amplified PCR that showed that the vast majority of the isolates belong to the same group (18). Figure 1 shows 11 isolates that display one major banding pattern. Once again, the predominance of a small number of strains at this centre suggests the likely mode of transmission is person to person, but does not rule out acquisition from some unknown environmental source. However, routine environmental infection control surveillance cultures to date have failed to yield any isolate of *B cepacia*.

**TABLE 1**  
**Factors associated with transmission of *Burkholderia cepacia* outside of hospital**

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| Kissing (reference 17)                   |
| Intimate contact (reference 17)          |
| Frequent social contact (reference 17)   |
| Hugging (reference 22)                   |
| Dancing (reference 22)                   |
| Sharing eating utensils (reference 22)   |
| Sleeping in the same room (reference 22) |

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The majority of the evidence to date points towards person-to-person transmission during close social contact. One postulated mechanism is inhalation of contaminated aerosol droplets. In one study, *B cepacia* could be isolated from the air in examining rooms occupied by colonized patients with aerosolized organisms remaining viable for almost 1 h (21). The number of organisms released into the air increased almost threefold with coughing. Further evidence in favour of person-to-person transmission was provided by Lipuma et al (16), who found that in most CF centres, over 50% of patients are colonized by the same strain and that the organism could not consistently be recovered from environmental samples. Additional evidence comes from CF summer camps. In 1990 in Ontario, 6% of cepacia-negative campers became colonized during or shortly after attending such a camp (22,23). All of the converters had the same strain and admitted to close contact with cepacia-positive participants. Only one of several environmental samples (sinks, showers, pond and lake water) yielded the organism, but that sample was shown by ribotyping to be distinct from that cultured from the sputum converters. In addition, the risk of colonization increased with a higher prevalence of cepacia-positive campers and with a longer stay at the camp. High risk situations identified from this investigation included close contact with a cepacia-positive camper such as dancing, sharing eating utensils and sleeping in the same cabin (22). Table 1 summarizes the major risk factors associated with transmission outside the hospital environment.

Govan et al (17) provided further evidence to support transmission through social contact. In the Edinburgh Adult Cystic Fibrosis Clinic, spread of an epidemic strain resulted in approximately 70% *B cepacia* colonization over a six-year period. Cross-infection among some patients was believed to have occurred during a weekly fitness class outside the hospital, although this was not proven and should be viewed as speculation. Similarly in the Manchester Adult CF Clinic, the same strain accounted for over 50% of *B cepacia* colonizations. Close social contact including "kissing under the mistletoe during Christmas festivities in the hospital" (17). Spread of the Edinburgh strain between patients from the two regional centres may have taken place during a weekend camp near Manchester five months before it was first isolated there. In fact, this particular strain is known as the 'transatlantic

**TABLE 2**  
**Factors associated with nosocomial transmission of *Burkholderia cepacia***

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| Cohorting of cystic fibrosis patients (reference 25)  |
| Hand shaking (reference 26)                           |
| Contaminated fomites (reference 27)                   |
| Contaminated respiratory equipment (references 28,29) |
| Lack of hand-washing (reference 29)                   |

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strain', because it has been shown by PFGE and sequencing of the cable pili (*cblA*) subunit gene to be identical to that of the predominant strain in Toronto (24). Transmission of the strain probably occurred at a summer camp in Ontario, but once again it remains unclear from which side of the Atlantic it originated.

### HOSPITALIZATION

Hospitalization is another risk factor for *B cepacia* acquisition in patients with CF (25). This most likely represents environmental contamination from cepacia-positive patients via contaminated surfaces, direct contact with colonized patients who are coughing, or the hands of health care workers. In fact, the organism can be transmitted through hand shaking for up to 3 h following contamination of the hands with colonized sputum (26). Case-control studies have identified respiratory equipment and having had a colonized roommate as risk factors for nosocomial acquisition (25). Outbreaks in health care institutions have been linked to patient cohorting and contaminated respiratory therapy equipment such as nebulizers, ventilator tubing and humidifiers (27).

Conly and colleagues (28) described an outbreak involving reusable thermometers contaminated by colonized calibration water. In another study, Hamill et al (29) reported epidemic transmission of *B cepacia* among hospitalized patients that was attributed to poor infection control practices (29). During that outbreak, the same vial of albuterol was used for multiple patients, in-line nebulizers might have been contaminated and regular hand-washing was neglected. Table 2 summarizes the factors associated with nosocomial transmission of *B cepacia*.

### INFECTION CONTROL IMPLICATIONS

The evidence presented above supports the policy of segregation of cepacia-positive and cepacia-negative patients, and in fact most CF treatment centres have adopted such a policy. In the United States, the Centers for Disease Control and Prevention, Atlanta, Georgia has recommended that strict contact isolation be implemented at CF summer camps that last longer than one week and in areas where the prevalence of *B cepacia* exceeds 5% (22). The International Cystic Fibrosis Foundation has an absolute exclusionary policy; participants at conferences must bring medical certification of cepacia- and methicillin-resistant *Staphylococcus aureus* (MRSA)-negative status. These measures have led to dramatic decreases in the

rate of new colonization (4,30). For example, at a CF paediatric centre in Glasgow in 1992, the rate of colonization with the organism dropped from 23 new cases (20%) to only three new cases over the ensuing 12 months following implementation of segregation in hospital (30). Similar strict infection control policies have been enforced at the Wellesley clinic since it was established in 1991. Between 1989 and 1991 in Toronto, 11 to 13 new colonizations per year occurred in approximately 500 paediatric and adult patients. In 1992, there were no cases of new cepacia acquisition. Since then, only three new cases have been reported at the Wellesley CF clinic. Two of these three patients had cepacia-positive siblings.

Specific infection control practices at this institution include scheduling out-patient visits on separate days for colonized and noncolonized patients (31). Sputum samples are collected from the noncolonized during every visit to the clinic to detect conversion, and recent converters are followed up closely with patient education and emotional support. Extensive decontamination protocols for respiratory equipment are followed after each clinic visit. On the in-patient CF ward, every effort is made to prevent unnecessary contact between cepacia-positive and -negative patients. For instance, all CF patients often have private rooms, and under no circumstances may colonized patients share a room with noncolonized patients. Separate showers are provided. Furthermore, to prevent cross-infection, there is no cohorting of CF patients with human immunodeficiency virus-positive patients or others infected by multiply resistant organisms such as MRSA or vancomycin-resistant enterococci. Patients are discouraged from visiting with one another. Environmental monitoring for contamination is carried out at regular intervals by collecting water samples from showers and drains, in addition to cultures from exercise equipment, physiotherapy equipment and pulse oximeters. Patient education programs focus on proper hygiene practices such as thorough hand-washing, covering the mouth when coughing and not sharing personal items such as handkerchiefs and toothbrushes.

Emotional and psychosocial issues have surfaced with the understanding that *B cepacia* may be transmitted from person to person in medical and social environments. Policy makers must bear in mind the implications of segregation for patients and their families in terms of limiting social interaction and decreasing emotional support. Support groups that have developed over years are being dismantled for fear of spreading *B cepacia* to noncolonized patients. The exclusionary policy of the International Cystic Fibrosis Foundation was mentioned above. It is not surprising that patients end up feeling isolated and fearful of either transmitting or acquiring infection. Much of the contention surrounding the issue of transmissibility is related to these issues because they affect the daily activities of patients so directly, both inside and out of the hospital setting. In the final analysis, because segregation and contact isolation policies require an enormous amount of cooperation and sacrifice on the part of CF patients, it must be ensured that policies are justified and supported by current scientific evidence in order to decrease the risk of premature death associated with *B cepacia*.

## CONCLUSIONS

*B cepacia* has recently been established as a major respiratory pathogen in patients with CF. Its virulence factors are poorly understood, but potential determinants include the production of cable and mesh pili, respiratory epithelial cell invasion, intracellular replication and resistance to many broad spectrum bacterial drugs. Colonization by this organism can be associated with a rapid decline in respiratory function and premature death, although clinical outcomes are often unpredictable. Evidence has accumulated to suggest that *B cepacia* can be transmitted from person to person. This is supported by preliminary data from the Wellesley Central Adult Cystic Fibrosis Clinic that indicate that over 90% of colonized patients harbour one of two major strains. Close social contact and hospitalization have been recognized as risk factors for cross-infection. For this reason, segregation policies according to colonization status are becoming widely accepted. Further research will expand our understanding of strain-related differences in the virulence and transmissibility of this organism. In addition, we need to develop techniques to isolate and identify highly transmissible strains of this pathogen better. Finally, we need to elucidate the relationship between certain bacterial genotypes and the different clinical outcomes of infection with *B cepacia*.

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