Infection control in cystic fibrosis: methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and the *Burkholderia cepacia* complex

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INTRODUCTION

In patients with cystic fibrosis (CF), chronic colonization with a narrow but evolving spectrum of bacterial pathogens, leading to intermittent episodes of debilitating inflammatory exacerbations and progressive lung damage, are major influences on quality of life and life expectancy. Emerging pathogens also tend to be inherently resistant to available antibiotics depriving patients of effective antibiotic therapy. Thus infection control plays a critical role in the management of CF lung disease.

ACQUISITION AND CROSS-INFECTION

Implementation of appropriate infection control must take account of two major modes of acquisition—namely, acquisition from natural environments or by cross-infection. Acquisition from natural environments requires knowledge of the sources and reservoirs of the infection control target. For example, whether or not the pathogen is a human commensal, such as *Haemophilus influenzae* which primarily infects the CF lung endogenously. Prevention of cross-infection acquired via patient-to-patient contact or nosocomial acquisition from contaminated equipment or hospital personnel requires consideration of possible routes of spread and bacterial survival on contaminated fomites. In the management of CF lung disease, cross-infection control requires implementation of basic hygiene and cross-infection control principles, but also has to take account of the nature of CF pathogens. Microbial factors relating to some CF pathogens might not be familiar to cross-infection control personnel in non-CF clinics. Furthermore, cross-infection control in CF patients has to take account not only of potential spread within CF centres but also spread by social contacts outside the hospital, and from environments that CF patients may encounter in everyday life. In considering the need for draconian measures, including strict segregation and exclusion from CF meetings, account should also be taken of the virulence and resistance of individual pathogens, and local conditions (for example, whether an 'epidemic' strain has been identified). Ideally, cross-infection control should be based on sound scientific evidence. Unfortunately, for ethical reasons it is often not possible to provide evidence based on human experiments. Infection control must then rely on judgements based on circumstantial evidence gained from accumulated epidemiological data. This issue is particularly relevant to the 'Can I do this?' type of scenario which shall be addressed later.

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Box 1 **Infection control targets in cystic fibrosis**

- *Staphylococcus aureus* and MRSA
- *Haemophilus influenzae*
- *Pseudomonas aeruginosa* and mucoid *P. aeruginosa*
- *Burkholderia cepacia* complex
- *Stenotrophomonas maltophilia*
- *Aspergillus fumigatus* and respiratory syncitial virus

INFECTION CONTROL TARGETS

The major microbial pathogens responsible for CF lung disease have been known for several decades and are listed in Box 1. *Staphylococcus aureus*, *H. influenzae* and *Pseudomonas aeruginosa* have been associated with CF lung disease since the first descriptions of CF in the 1940s. From the late 1980s, onwards, *Burkholderia cepacia*, or more correctly members of the *B. cepacia* complex, have emerged as major pathogens. *Stenotrophomonas maltophilia* and atypical mycobacteria are being isolated with increased frequency in some centres but the clinical significance of these microbes is unclear. This article will focus on the major pathogens associated with cross-infection namely, methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* and *B. cepacia*.

Staph. aureus and MRSA

Staph. aureus colonizes the upper respiratory tract, in particular the anterior nares, of approximately 40%–50% of healthy humans. Thus, most but not all pulmonary infections in CF individuals result from endogenous infection from the patient's own organism. The situation with MRSA requires more careful consideration and brings

in the criteria of virulence, transmissibility and resistance referred to earlier. At present, the incidence of MRSA in CF patients is relatively low and the clinical importance of these organisms in CF patients is doubtful[1–3]. In terms of infection control of MRSA in CF, implementation of non-CF guidelines should be followed including close attention to personal hygiene by patients and nursing staff[4–8]. Attendance of CF individuals colonized with MRSA at meetings and outings is not recommended.

P. aeruginosa and mucoid *P. aeruginosa*

P. aeruginosa remains the major CF pathogen with a worldwide prevalence which rises to 80%–90% in CF adults[2,3,9]. The onset of chronic colonization is associated with acceleration of forced expiratory volume in 1 s (FEV_1) decline[10] and has been described as the 'point of no return'[11]. This poor prognosis is particularly relevant to the transformation of the original colonizing strain into the mucoid colonial form which is due to copious production of a highly viscid exopolysaccharide, known as alginate[9,12]. I will return to a possible link between the potential for cross-infection and transformation to the mucoid colonial form later in this review.

In the last two decades, aggressive early therapy with colistin and ciprofloxacin has gained increasing recognition as a successful and strategic therapy to eliminate initial colonization and delay the chronic infection. Evidence to show that spread of *P. aeruginosa* occurs in the home, in CF-clinics or at summer camps has been scanty. Hence, the issue of infection controls against *P. aeruginosa*, and in particular segregation of colonized individuals from other CF patients, has remained controversial.

Several early studies showed that *P. aeruginosa* cross-infection can occur between CF siblings[13,14] but also that such colonization was often transient and did not necessarily lead to chronic infection[15]. Another explanation is that siblings acquire the same strain from a common source within the home. Other studies showed that most unrelated CF patients retain their own individual strain for long periods[14] and that cross-infection in CF centres is relatively rare[16–18]. Similarly, the risk associated with attendance at camps was reported to be comparable to that occurring in the community[19,20]. Acquisition from hospital sites or environment was suggested by several groups[21–23] but found to be low[24,25]. By the early 1990s, most studies indicated that unrelated CF patients tend to be chronically colonized by distinct genomic types indicating a low incidence of patient-to-patient spread or acquisition from a common source.

However, Tummler *et al.* reported that over a 4-year period 12/40 (60%) of patients attending camps, clinics and rehabilitation in the Hanover region shared the same clone[26]. Other studies provided circumstantial evidence for cross-infection by demonstrating an increased incidence of new cases in centres with high *P. aeruginosa* carriage[27] and a higher incidence in CF clinics compared with non-specialist centres[28].

A key feature of these conflicting studies is the need to balance circumstantial evidence for cross-infection with scientific evidence for spread of a single clone. In a recent study using arbitrarily primed-polymerase chain reaction (AP-PCR) fingerprinting, the majority of patients were found to be colonized with their own unique strain over a period of 3 years. However, it was noted that patients from the same family or attending the same school tended to harbour the same clone[29]. Sharing of similar clones could result from either patient-to-patient spread or acquisition from a common environmental source. An interesting case of the latter was the use of phenotypic and genomic fingerprinting to demonstrate acquisition of a particular strain of *P. aeruginosa* from a hydrotherapy pool[30]. In this episode, two unrelated, and previously non-colonized CF patients, acquired the same nonmucoid strain of *P. aeruginosa* after sharing a single session in the pool. The assumed, but seldom documented, link between non-mucoid and mucoid forms of *P. aeruginosa* was confirmed when, within 3 months, a mucoid form of the same strain was cultured from one of the patients. Sampling of the pool revealed the colonizing strain and four other clones. Subsequent comparative studies showed the colonizing strain to be significantly more mucinophilic and chemotactic than the other strains recovered from the pool supporting the hypothesis that these properties, in association with impaired mucociliary clearance, play an important role in the initial stages of pulmonary colonization in patients with CF[3,31–33]. This raises the question of whether particular subpopulations of *P. aeruginosa* have a predilection for the CF lung and are associated with a worse prognosis. Early data from pyocin typing had suggested that subpopulations of *P. aeruginosa* might exist with a predilection for pulmonary colonization in patients with CF and other chronic airways diseases[34]. A more recent study suggests that particular clones, identified by AP-PCR fingerprinting, can be associated with increased severity of lung disease[29].

In 1993, the report[17] of a working party organized by the French CF Association (Association Française de Lutte contre la Mucoviscidose) to provide a consensus on the epidemiology of *P. aeruginosa* in CF concluded:

> 'Although cross infection with *P. aeruginosa* does not seem to be a major problem cross-colonization and epidemic spread of multidrug-resistant *P. aeruginosa* between CF patients has been observed in some studies.'

The principal evidence for cross-infection in this report, other than already suggested in siblings, was based on

Danish studies which showed that spread of multiresistant *P. aeruginosa* was reduced by segregation[22]. However, although transmission may have been prevented by segregation, the Danish evidence for clonal spread was based on serotyping and phage typing—systems known to be of limited value for fingerprinting the mucoid, polyagglutinating and LPS-defective isolates characteristic of prolonged colonization in CF patients. Recently, however, two independent genomic fingerprinting techniques, pulse-field gel electrophoresis and flagellar polymorphisms, provided the first compelling evidence of large-scale spread in a CF centre[35]. In this study of 120 CF patients, 92 (77%) were *P. aeruginosa* positive and 65 harboured the same multiresistant strain. The results obtained with the two typing systems were concordant. Interestingly, it is likely that the outbreak would not have been discovered had the centre not enrolled patients in large multicentred antibiotic trial—a situation which emphasizes the need for surveillance in the prevention and control of *P. aeruginosa* cross-infection in all CF centres.

In conclusion, there is clear evidence that *P. aeruginosa* can be transmitted between CF siblings and, less frequently, that epidemic spread of multiresistant forms is possible amongst unrelated CF patients. Because segregation of *P. aeruginosa* positive patients remains controversial, and may not be logistically possible in some centres, it is essential that infection control measures against *P. aeruginosa* should include ongoing surveillance to identify episodes of cross-infection and allow appropriate action to be taken. For this purpose, the CF Trust has set up the Edinburgh CF Microbiology Laboratory and Strain Repository under the directorship of the author (details available from the CF Trust). The function of the Edinburgh laboratory is to augment the facilities provided by the Public Health Laboratory Service laboratory at Colindale by providing a range of services including preservation of epidemic clones and identification and typing facilities.

Why is transmission of *P. aeruginosa* not more common?

Before leaving the subject of *P. aeruginosa* cross-infection, it is interesting to consider why transmission of this most prevalent of all CF pathogens is relatively uncommon, and usually restricted to sibling contacts. In non-CF patients, epidemic spread of *P. aeruginosa* is well recognized. Indeed, attention to hygiene and cross-infection control, has played a major part in the reduction of life-threatening *P. aeruginosa* infections in patients immunocompromised by burns or neutropenia. One explanation for the relatively low transmission in CF patients could be the characteristic phenotypic changes associated with adaptation to the CF lung environment: namely the transformation of typical nonmucoid *P. aeruginosa*, expressing an armoury of virulence determinants (motility, adhesins, proteases, exotoxins, smooth LPS), to a biofilm-embedded mucoid form in which most of these characteristics have been suppressed[9]. Looked at in another way, we see a highly transmissible free-living saprophytic bacterium transforming to a poorly transmissible parasite.

Burkholderia cepacia

Based on potential virulence, transmissibility and resistance, *B. cepacia* holds the CF community to ransom more than any other pathogen. In 1984, the seminal paper by Isles *et al.*[36] described what is now referred to as cepacia syndrome—a rapidly fatal necrotizing pneumonia, sometimes accompanied by septicaemia which occurs in approximately 30% of colonized CF patients. After initial reluctance to consider the organism as anything more than a marker of progressive lung disease, there is now consensus that these soil bacteria present a real threat to the CF community. Anxiety stems from several factors which are summarized briefly: (1) unexpected clinical decline even in CF patients with good lung function; (2) epidemic spread amongst unrelated CF patients both within CF clinics and during social contacts; and (3) inability to forecast clinical outcome even when a group of patients are colonized with the same *B. cepacia* strain. These issues have been recently reviewed[3,37,38]. An attempt has also been made to answer some of the questions which are frequently raised by patients concerning this relatively unusual group of bacteria[39]. Before we consider infection control measures against *B. cepacia*, it is important to consider recent progress in the laboratory identification, epidemiology, transmissibility and pathogenic potential of this unusual and a diverse group of bacteria, which until now have been called simply, *B. cepacia*.

Integrated genotypic and phenotypic analyses have shown that isolates presumptively identified by conventional laboratory tests as *B. cepacia*, belong to a diverse group of organisms comprising at least six genomic species (genomovars); these are now referred to as the *B. cepacia* complex[40]. At present, the complex comprises genomovar I (which contains the type strain and by convention retains the species title, *B. cepacia*), genomovar II (renamed *B. multivorans*), genomovar III, genomovar IV (renamed *B. stabilis*), genomovar V (renamed *B. vietnamiensis*) and genomovar VI. All members of the complex have been cultured from CF patients. However, *B. multivorans*, and in particular genomovar III, are associated with virulence and epidemic spread. Spread may be confined to a single CF centre or involve patients at a national and international level. The notorious ET12 lineage[37,41] is widespread in Canada and the UK and, in the early 1990s, accounted for almost 50% of all isolates in the latter[42]. Bacterial factors

Box 2 **Epidemiology of *Burkholderia cepacia* in a large cystic fibrosis (CF) clinic (Ref 51)**

- Prevalence: 85 of 769 patients (11%)
- Outcome varied from asymptomatic to fatal septicaemia even with the same strain
- Transmission between unrelated CF schoolmates but in only three of eight pairs of CF siblings
- Despite segregation 15 new cases in 1993

Box 3 **Contentious issues in the management of *Burkholderia cepacia* transmission**

- Cohorting of *B. cepacia*$^{+}$ patients—risk of acquiring a second strain?
- Transient carriers and patients who are culture negative but polymerase chain reaction positive—should they be segregated?
- Risk of transmission to non-cystic fibrosis individuals
- Are some *B. cepacia* more dangerous than others?
- What are the routes of transmission?

associated with increased transmissibility include an unusual form of cable pili associated with enhanced adhesion to respiratory mucin[41,43–45] and a chromosomal marker, of unknown function, called the *B. cepacia* epidemic strain marker (bcesm) [46,47]. Most but not all epidemic, strains possess bcesm. Furthermore, the transatlantic clone ET12 is almost unique in possessing both bcesm and cable pili[47]. Until more evidence is available, all members of the *B. cepacia* complex should be treated as potential human pathogens.

Infection control against *B. cepacia*

Infection control against *B. cepacia* requires segregation and careful surveillance involving selective culture and reliable identification[38,48–50]. It is also important to accept that whilst segregation has reduced the incidence of patient-to-patient spread it does eliminate sporadic new cases of infection from natural environments[37,51] (Box 2). Infection control measures, thought to be adequate in the early 1990s, may need to be revised and difficult decisions made[52] (Box 3). For example, cohorting of colonized patients may increase the risk of superinfection by epidemic strains with fatal consequences[53]. The risk of superinfection is particularly relevant if CF patients are exposed to other patients colonized with what is often referred to as 'the epidemic strain', namely the intercontinental genomovar III lineage, ET12[37]. This raises the question of how much we can generalize on '*B. cepacia*'. Future studies may reveal that contentious issues such as transient colonization (unusual when epidemic strains are involved), the variable impact of *B. cepacia* on post transplantation[54], and the 30% incidence of 'cepacia syndrome'[36–48], may not apply to all members of the *B. cepacia* complex but be heavily influenced by the impact of genomovars II and III, and in particular by the spread of ET12 and other epidemic genomovar III clones[55,56]. This strain-specific influence explains the rare, but documented, case of bronchiectasis in a non-CF parent exposed to her colonized CF children[57].

Finally, we can turn to the type of question faced by many CF carers and microbiologists: namely, the 'Can I do this scenario?' When 'this' ranges from: (1) cross-infection risks—shared car journeys, short-term visits involving CF patients, non-CF patients, relatives, health visitors; and (2) 'environmental risks'—air travel, digging in the garden, botanical trips to the local pond, etc. At present, there are no simple scientifically valid answers to such questions. Instead, Solomon-like judgements must rely on risk assessment and published guidelines[58] which are in turn based on present knowledge of the natural habitats,

Box 4 **Bacterial factors relevant to transmission of *Burkholderia cepacia***

- No gut or commensal carriage
- Low aerosol recovery
- Sensitive to disinfectants at recommended strengths
- High sputum and salivary counts in colonized patients
- Survival on skin up to 30 min, sputum contamination of surfaces up to a week, in water for years
- Strain-specific transmission

Box 5 **Activities between colonized and non-colonized cystic fibrosis patients carrying high risk of transmission** [Adapted from Cystic Fibrosis Trust Guidelines on *Burkholderia cepacia* 1999[58] (Ref 58)]

- Contacts involving siblings
- Close social contact—sharing bedrooms, evenings in pub or restaurant
- Hand shaking
- Contacts allowing exchange of respiratory secretions—kissing, hand shaking without handwashing
- Extended travelling together in confined conditions—e.g. car, plane
- Sports or exercise classes
- Sharing drinking and eating utensils
- Intimate contacts—kissing, sexual relationships

virulence, epidemiology and survival of *B. cepacia*[37–39,59] (Boxes 4, 5). Clinical judgements on appropriate infection control can then be modified by awareness of the *B. cepacia* population within an individual clinic, by what is logistically achievable in individual CF centres, and most important, by what is reasonable and acceptable to the individual CF patient.

REFERENCES

1 Boxerbaum B, Jacobs MR, Cechner RL. Prevalence and significance of methicillin-resistant *Staphylococcus aureus* in patients with cystic fibrosis. *Pediatr Pulmonol* 1988;**4**:159–63

2 Gilligan PH. Microbiology of airway disease in patients with cystic fibrosis. *Clin Microbiol Rev* 1991;**4**:35–51

3 Hutchison MI, Govan JRW. Pathogenicity of microbes associated with cystic fibrosis. *Microb Infect* 1991;**1**:1005–14

4 Duckworth G, Heathcock R. Guidelines on the control of methicillin-resistant *Staphylococcus* in the community. *J Hosp Infect* 1995;**31**:1–12

5 Lessing MP, Jordens JZ, Bowler IC. When should health care workers be screened for methicillin resistant *Staphylococcus aureus*? *J Hosp Infect* 1996;**34**:205–10

6 Cox RA, Conquest C. Strategies for the management of healthcare staff colonised with epidemic methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 1997;**35**:117–27

7 Centers for Disease Control and Prevention. Interim guidelines for prevention and control of staphylococcal infection associated with reduced susceptibility to vancomycin. *Morb Mortal Wkly Rep* 1997; **46**:626–35

8 Austin DJ, Anderson RM. Transmission dynamics of epidemic methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in England and Wales. *J Infect Dis* 1999;**179**:883–91

9 Govan JRW, Deretic V. Microbial pathogenesis in cystic fibrosis: mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia*. *Microbiol Rev* 1996;**60**:539–74

10 Pamucki A. Bush A, Buchdahl R. Effects of *Pseudomonas aeruginosa* colonization on lung function and anthropomorphic variables in children with cystic fibrosis. *Pediatr Pulmonol* 1995;**19**:10–15

11 Drittanti L, Masciovecchio MV, Gabbarini J, Vega M. Cystic fibrosis: gene therapy or preventive gene transfer. *Gene Therapy* 1997;**4**:1001–3

12 Henry RL, Mellis CM, Petrovic L. Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. *Pediatr Pulmonol* 1992;**12**:158–61

13 Grothues D, Kopman U, von der Hardt H, Tummler B. Genome fingerprinting of *Pseudomonas aeruginosa* indicates colonization of cystic fibrosis siblings with closely related strains. *J Clin Microbiol* 1988;**26**:1973–7

14 Kubesch P, Linger M, Grothues D, Wehsling M, Tummler B. Strategies of *Pseudomonas aeruginosa* to colonize and to persist in the cystic fibrosis lung. *Scand J Gastroenterol* 1988;**143**(suppl):77–80

15 Renders NH, Sijmons MA, van Belkum A, Overbeek SE, Mouton JW, Verbrugh HA. Exchange of *Pseudomonas aeruginosa* strains among cystic fibrosis siblings. *Res Microbiol* 1997;**148**:447–54

16 Speert DP, Campbell ME. Hospital epidemiology of *Pseudomonas aeruginosa* from patients with cystic fibrosis. *J Hosp Infect* 1987;**9**:11–21

17 Bingen E, Botzenhardt K, Chabanon G, Döring G, Govan J, Høiby N, *et al.* In: Doring G, Schaffer L, eds. *Epidemiology of Pulmonary Infections By* Pseudomonas *in Patients With Cystic Fibrosis: a Consensus Report*. Paris: Association Française de Lutte contre la Mucoviscidose, 1993

18 Campbell ME, Mahenthiralinagm E, Henry D, Speert DP. Analysis of the epidemiology of *Pseudomonas aeruginosa* colonization in patients with cystic fibrosis using randomly amplified polymorphic DNA fingerprinting [Abstract 434]. *Pediatr Pulmonol* 1998;suppl 17:326

19 Speert DP, Lawton D, Damm S. Communicability of *Pseudomonas aeruginosa* in a cystic fibrosis summer camp. *J Pediatr* 1982;**101**: 227–9

20 Hoogkmp-Korstanje JA, Meis JA, Kissing J, van der Laag J, Melchers JW. Risk of cross colonization and infection by *Pseudomonas aeruginosa* in a holiday camp for cystic fibrosis patients. *J Clin Microbiol* 1995;**33**:572–5

21 Aycliff GA, Babb JR, Collin BJ, Lowbury EJL, Newsom SWB. *Pseudomonas aeruginosa* in hospital sinks. *Lancet* 1974;**i**:578–81

22 Pedersen SS, Koch C, Hoiby N, Rosendal K. An epidemic spread of multiresistant *Pseudomonas aeruginosa* in a cystic fibrosis centre. *J Antimicrob Chemother* 1986;**17**:505–16

23 Doring G, Ulrich M, Muller W, Bitzer J, Schidt-Koenig L, Must L, *et al.* Generation of *Pseudomonas aeruginosa* aerosols during hand washing from contaminated sink drains, transmission to hands of hospital personnel and its prevention by use of a new heating device. *Z Hyg* 1991;**110**:427–36

24 Jensen ET, Giwercman B, Ojeniyi B, Bangsborg JM, Hansen A, Koch C, *et al.* Epidemiology of *Pseudomonas aeruginosa* in cystic fibrosis and the possible role of contamination by dental equipment. *J Hosp Infect* 1997;**36**:117–2

25 Zembrzuska-Sadkowska E, Sneum M, Ojeniyi B, Heiden L, Hoiby N. Epidemiology of *Pseudomonas aeruginosa* infection and the role of contamination of the environment in the Danish Cystic Fibrosis Centre. *J Hosp Infect* 1995;**29**:1–7

26 Tummler B, Kooperman U, Gruthues D, Weissbrodt H, Steinkamp G, von der Hardt H. Nosocomial acquisition of *Pseudomonas aeruginosa* by cystic fibrosis patients. *J Clin Microbiol* 1991;**29**:1265–7

27 Farrell PM, Guanghong S, Splaingard M, Colby CE, Loxova A, Kosorok MR, *et al.* Acquisition of *Pseudomonas aeruginosa* in children with cystic fibrosis. *Pediatrics* 1997;**100**:21–9

28 Mahadeva R, Webb K, Westerbeek RC, Carroll NR, Dodd M, Bilton D. Clinical outcome in relation care in centres specialising in cystic fibrosis: cross sectional study. *BMJ* 1998;**346**:1771–5

29 Adams C, Morris-Quinn M, McConnell F, West J, Lucey B, Short C, *et al.* Epidemiology and clinical impact of *Pseudomonas aeruginosa* infection in cystic fibrosis using AP-PCR fingerprinting. *J Infect* 1998;**37**:151–8

30 Govan JRW, Nelson JW. Microbiology of lung disease in cystic fibrosis. *Br Med Bull* 1992;**48**:912–30

31 Nelson JW, Tredgett MW, Sheehan JK, Thornton DJ, Notman D, Govan JRW. Mucinophilic and chemotactic properties of *Pseudomonas aeruginosa* in relation to pulmonary colonization in cystic fibrosis. *Infect Immunol* 1990;**58**:1489–95

32 Matsui H, Grubb BR, Tarran R, Randell SH, Gatzy JT, Davis CW, Boucher RC. Evidence for perciliary liquid layer depletion, not abnormal ion composition, in the pathogenesis of cystic fibrosis airways disease. *Cell* 1998;**95**:1005–15

33 Boucher RC. Molecular insights into the physiology of the thin film of airway surface liquid. *J Physiol (Lond)* 1999;**516**:631–8

34 Tredgett MW, Doherty C, Govan JRW. Incidence of common pyocin types of *Pseudomonas aeruginosa* from patients with cystic fibrosis and chronic airways diseases. *J Med Microbiol* 1999;**32**:169–72

35 Cheng K, Smyth RL, Govan JRW, Doherty C, Winstanley C, Denning N, *et al.* Spread of b-lactan-resistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. *Lancet* 1996;**348**:639–42

36 Isles JA, McLusky I, Corey M. *Pseudomonas cepacia* infection in cystic fibrosis: an emerging problem. *J Pediatr* 1984;**104**:206–10

37 Govan JRW, Hughes J, Vandamme P. *Burkholderia cepacia*: medical, taxonomic and ecological issues. *J Med Microbiol* 1996;**45**:395–7

38 LiPuma JJ. *Burkholderia cepacia*: management issues and new insights. *Clin Chest Med* 1998;**19**:473–86

39 Govan JRW, Burns JL, Speert DP. Common questions about *Burkholderia cepacia*. *Int Assoc Cystic Fibrosis Adults* 1999;**55**:3–11

40 Vandamme P, Holmes B, Vancanneyt TM, Coenye T, Hoste B, Coopman R, *et al.* Occurrence of multiple genomovars of *Burkholderia cepacia* in cystic fibrosis patients and proposal of *Burkholderia multivorans* sp. nov. *Int J Syst Bacteriol* 1997;**47**:1188–2000

41 Sun L, Jiang R-Z, Steinbach S, Holmes A, Campanelli C, Forstner J, *et al.* The emergence of a highly transmissible lineage of *cbl*$^{+}$ *Pseudomonas (Burkholderia) cepacia* causing CF centre epidemics in North America and Britain. *Nature Med* 1995;**1**:661–6

42 Pitt TL, Kaufmann ME, Patel PS, Bege LC, Gaskin S, Livermore DM. Type characterisation and antibiotic susceptibility of Burkholderia (*Pseudomonas*) *cepacia* isolates from patients with cystic fibrosis in the United Kingdom and the Republic of Ireland. *J Med Microbiol* 1996;**44**:103–10

43 Sajjan US, Forstner JF. Identification of the mucin binding adhesin of *Pseudomonas cepacia* isolated from patients with cystic fibrosis. *Infect Immunol* 1992;**60**:1434–40

44 Sajjan US, Corey M, Karmail MA, Forstner JK. Binding of *Pseudomonas cepacia* to normal human intestinal mucin and respiratory mucin from patients with cystic fibrosis. *J Clin Invest* 1992;**89**:648–56

45 Sajjan US, Sun L, Goldstein R, Forstner JF. Cable (cbl) type II pili of cystic fibrosis-associated *Burkholderia (Pseudomonas) cepacia*: nucleotide sequence of *cbl*A major sub unit pilin gene and novel morphology of the assembled appendage. *J Bacteriol* 1995;**177**:1030–8

46 Mahenthiralingam E, Simpson DA, Speert DP. Identification and characterization of a novel DNA marker associated with epidemic strains of *Burkholderia cepacia* recovered from patients with cystic fibrosis. *J Clin Microbiol* 1997;**35**:808–16

47 Mahenthiralingam E, Coenye T, Chung J, Speert DP, Govan JRW, Vandamme P. A diagnostically and experimentally useful panel of strains from the *Burkholderia cepacia* complex. *J Clin Microbiol* 2000,**38**:910–13

48 Pitt TL, Govan JRW. *Pseudomonas cepacia* and cystic fibrosis. *PHLS Microbiol Digest* 1993;**10**:69–72

49 Henry DA, Campbell ME, LiPuma JJ, Speert DP. Identification of *Burkholderia cepacia* isolates from patients with cystic fibrosis and use of a simple selective medium. *J Clin Microbiol* 1997;**35**:614–19

50 Henry DD, Campbell ME, McGimpsey C, Clarke A, Louden L, Burns JL, *et al.* Comparison of isolation media for recovery of *Burkholderia cepacia* complex from respiratory secretions of patients with cystic fibrosis. *J Clin Microbiol* 1999;**37**:1004–8

51 Cazzola G, Amalfitano G, Tonelli E, Perazzoli C, Piacentini I, Mastella G. *Burkholderia (Pseudomonas) cepacia* epidemiology in cystic fibrosis population: a genome fingerprinting study. *Acta Paediatr* 1996;**85**: 554–7

52 Webb AK, Govan JRW. *Burkholderia cepacia*: another twist and a further threat. *Thorax* 1998;**53**:333–4

53 Ledson MJ, Gallagher MJ, Corkhill JE, Hart CA, Walshaw MJ. Cross infection between cystic fibrosis patients colonised with *Burkholderia cepacia*. *Thorax* 1998b;**53**:432–6

54 Webb AK, Egan J. Should patients infected with *Burkholderia cepacia* undergo lung transplantation. *Thorax* 1997;**52**:671–3

55 Govan JRW, Brown PH, Maddison J, Doherty CJ, Nelson JW, Dodd M, *et al.* Evidence for transmission of *Pseudomonas cepacia* by social contact in cystic fibrosis. *Lancet* 1993;**342**:15–19

56 Holmes A, Nolan R, Taylor R, Finley R, Riley M, Jiang RA, *et al.* An epidemic of *Burkholderia cepacia* transmitted between patients with and without cystic fibrosis. *J Infect Dis* 1999;**179**:1197–205

57 Ledson MJ, Gallagher MJ, Walshaw MJ. Chronic *Burkholderia cepacia* bronchiectasis in a non-cystic fibrosis individual. *Thorax* 1998a;**53**: 430–2

58 Cystic Fibrosis Trust Infection Control Group. *Burkholderia cepacia.* London: Cystic Fibrosis Trust, 1999

59 Drabick JA, Gracey EJ, Heidecker GJ, Liluma JJ. Survival of *Burkholderia cepacia* on environmental surfaces. *J Hosp Infect* 1996;**32**:267–76