

# Infection with *Burkholderia cepacia* in Cystic Fibrosis Outcome Following Lung Transplantation

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As a result of concern over excessive mortality after lung transplantation, many transplant programs refuse to accept cystic fibrosis (CF) patients infected with *Burkholderia cepacia*. As a significant proportion of patients with CF in our community are infected with this organism, we have continued to provide lung transplantation as an option. A retrospective review was conducted of medical records of all patients with CF transplanted between March 1988 and September 1996. Fifty-six transplant procedures were performed in 53 recipients with CF between March 1988 and September 1996. Twenty-eight had *B. cepacia* isolated pretransplant and 25 remaining positive post-transplant. Of the 53 recipients, 19 have died (15 of 28 [54%] *B. cepacia* positive and 4 of 25 [16%] *B. cepacia* negative). *B. cepacia* was responsible for or involved in 14 deaths. Nine of the deaths occurred in the first 3 mo post-transplantation. One-year survival was 67% for *B. cepacia* positive patients and 92% for *B. cepacia* negative patients. Recent modifications in antimicrobial and immunosuppressive therapy since 1995 have resulted in no deaths early post-transplant in the last five patients transplanted. We conclude that early mortality in patients with CF infected with *B. cepacia* is significantly higher than in those not infected with *B. cepacia*. Modifications in post-transplant medical therapy may improve outcome.

Advanced lung disease secondary to cystic fibrosis (CF) is characterized by a state of chronic respiratory infection that is frequently associated with organisms resistant to multiple antibiotics. Following the success of combined heart and lung transplantation for CF (1, 2), bilateral lung transplantation has been shown to be an acceptable and perhaps the preferred surgical option for end-stage lung disease from CF. Indeed, both short- and long-term survival are similar to those patients transplanted for lung diseases other than CF (3, 4).

Although the CF gene has been identified and the basic defect in the airway epithelium has been shown to be chloride impermeability, it is still not clear how this leads to the specific bacterial affinity, infection, and inflammation in the CF lung. Several hypotheses have been proposed to explain the pathogenesis of CF lung disease, including increased receptors to *Pseudomonas aeruginosa* on respiratory epithelial cells in CF (5) and defective cellular uptake of *P. aeruginosa* (6). Although there is still debate about the composition of airway surface fluid in CF, the concentration of NaCl may affect bacterial killing by defensins (7).

The most common organism in the lungs and sinuses of people with CF is *P. aeruginosa*. Other typical CF organisms include *Staphylococcus aureus*, *Haemophilus influenzae*, and *Burkholderia cepacia*. Less commonly, the late stages of lung disease may be accompanied by the presence of *Stenotroph-*

*omonas maltophilia*, *Alcaligenes xiloxidans*, and nontuberculous mycobacteria such as *Mycobacterium avium* complex (MAC) or *Mycobacterium abscessus*. *B. cepacia* has been associated with a higher mortality both before and after lung transplantation (8–12). As a result of adverse outcomes after transplantation, many centers have reevaluated their criteria and have chosen not to offer transplantation to those patients with CF who are known to harbor *B. cepacia* in the presence of resistance to multiple antibiotics (13–15).

For those few programs that continue to accept candidates who are known to be infected with *B. cepacia*, lung transplantation represents a considerable challenge to the transplant teams. In the Toronto Lung Transplant Program we have perhaps the largest group of lung transplanted patients infected with *B. cepacia*. Our initial experience suggested a high mortality after transplantation when this organism was present (16, 17). While we continue to reevaluate our policy to accept such candidates, we have continued to offer transplantation when the usual preoperative criteria have been met. We therefore wish to share our additional experience with lung transplantation in these very challenging patients.

## METHODS

### Study Design

A retrospective review of medical records was conducted of all recipients of lung transplants performed for CF in the Toronto Lung Transplant Program between March 1988 and September 1996. The review of medical records and microbiologic evaluations of sputum included those from the referring center wherever possible. The microbiology laboratories at The Toronto Hospital, the Wellesley Hospital, and the Hospital for Sick Children specifically examine for *B. cepacia* in sputum samples from individuals with CF. The latter two centers constitute the referral base for the vast majority of patients with CF to the Toronto Lung Transplant Program. The Toronto Hospital has used *B. cepacia* selective media since 1991 whereas the other two centers incorporated *B. cepacia* selective media before 1991. Documentation of sputum culture results included samples from the closest time to referral to the transplant program. Cultures following lung transplantation (both sputum and bronchoalveolar lavage [BAL]) were tested for *B. cepacia* and recorded.

Infectious complications, incidence of bronchiolitis obliterans (BO), survival, and causes of death were documented in all CF lung transplant recipients.

### Lung Transplant Selection Criteria

Criteria for acceptance for lung transplantation have been published elsewhere (18). No potential recipient was denied the opportunity of lung transplantation based only on positive sputum cultures for *B. cepacia*.

### *B. cepacia* Infection

Those candidates who had cultures indicating *B. cepacia* in at least two sputum samples at some point before transplantation, including all available records prior to referral to the transplant program, were included in the population of recipients who were categorized as having chronic infection with *B. cepacia*.

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**Immunosuppression Protocol**

Cyclosporine was given intravenously immediately after transplantation. Conversion to oral dosing was usually done between Days 3 and 7. Cyclosporine dosing was adjusted to maintain a whole blood level between 250 and 350 ng/ml. Azathioprine was administered at 1.5 mg/kg/d either intravenously or orally. Methylprednisolone 500 mg was administered intravenously before reperfusion during the operation, followed by prednisone 0.8 mg/kg/d. Medication dosing and levels were maintained as shown in Table 1. From November 1983 to January 1993, all recipients received cytolytic induction therapy during the first 5 to 7 d. Between January 1993 and August 1995, patients were randomized to placebo or induction cytolytic therapy for 7 d. As this is a double-blind study, the code has not as yet been revealed. During that period, nine recipients with *B. cepacia* were transplanted. Since September 1995, our immunosuppression protocol was altered only for those with *B. cepacia* because of the high mortality we observed. For these recipients cyclosporine concentrations were kept between 250 and 300 µg/ml during the first 6 mo and azathioprine was given at 1 mg/kg/d. Antilymphocytic products are no longer administered to these patients.

**Infection Prophylaxis**

**Bacterial infection.** Before September 1995, all recipients with CF received treatment with at least two antipseudomonas antibiotics (usually a third-generation cephalosporin [ceftazidime] and an aminoglycoside) for approximately 10 to 14 d post-transplant. Because of the high posttransplant mortality observed in patients with *B. cepacia* infection, an alternative antimicrobial regimen was introduced. Since September 1995 we have prescribed ceftazidime 2 g intravenously every 8 h, chloramphenicol 500 mg intravenously every 6 h, tobramycin 5 mg/kg intravenously daily, trimethoprim-sulfamethoxazole (TMS) 320 mg/1,600 mg, every 12 h, and tobramycin inhalations 160 mg every 8 h, and after extubation 80 mg every 8 h for 3 mo after transplantation.

**Cytomegalovirus (CMV) prophylaxis.** Since 1991, ganciclovir and hyperimmune globulin have been administered if the recipient or donor had positive CMV serology. Dosing was as follows: ganciclovir 5 mg/kg every 12 h for the first 14 d, followed by 5 mg/kg/d 3 times a week for 12 additional weeks; and CMV hyperimmune globulin 150 mg/kg once during the first 48 h and again after 2 wk, then 100 mg/kg on Weeks 4, 6, 8, 12, and 16. Before 1997, the CMV hyperimmune globulin was produced by the Canadian Red Cross Society and was obtained from blood donors with high titers of CMV under the name "GamimmuneN." Since September 1997, the Canadian Blood Services have used Cytogam (Massachusetts Public Health Biologic Laboratories, Boston, MA). Patients who were CMV donor and recipient negative received acyclovir 400 mg every 8 h for a period of 3 mo for prophylaxis against herpes virus.

**Pneumocystis carinii prophylaxis.** By the second week, all transplant recipients received TMS prophylaxis. For those patients allergic to TMS, either dapsone with trimethoprim or inhaled pentamidine have been prescribed.

**Surveillance for Infection and Rejection**

Sputum cultures were performed as clinically indicated while patients were pending transplantation, immediately before transplantation, and after transplantation. Cultures were processed from all bronchoscopy specimens (both for surveillance purposes and for clinical indications). During the early postoperative period, endotracheal suctioning specimens were cultured if they appeared purulent or if the recipient was having symptoms or signs consistent with infection.

Surveillance bronchoscopy with BAL and transbronchial biopsies (TBB) was performed between Weeks 1 to 3, at Week 6, at Months 3, 6, 9, 12, 18, and 24, and yearly thereafter. Bronchoscopy was also performed whenever clinical signs or symptoms suggested the possibility of rejection.

BAL and sputum samples were sent for bacterial cultures. In patients with CF they were cultured specifically for *B. cepacia* using OF-PBL (19) (oxidation-fermentation base supplemented with agar, lactose, polymyxin B sulfate [Colistin] and Bacitracin) media, which was incubated at 30° C but always less than 35° C for 3 to 5 d. Susceptibilities to antimicrobial agents were determined by a microscan microtiter automated susceptibility assay (Dade International Inc., West Sacramento, CA) using both automated and manual detection of growth.

**Antibiotic Sensitivities**

The following antibiotic sensitivities were assessed at The Toronto Hospital: gentamicin, tobramycin, piperacillin, ciprofloxacin, TMS, ticarcillin, and ceftazidime were assessed on a first run. The antibiotic sensitivities requested also included amikacin, chloramphenicol, and imipenem when specifically requested or when the initial sensitivity results indicated resistance to the previously mentioned antibiotics.

The following antibiotics sensitivities were assessed at the Wellesley Hospital and Hospital for Sick Children: ceftazidime, piperacillin, tobramycin, amikacin, aztreonam, meropenem, ciprofloxacin, chloramphenicol, TMS, ticarcillin, doxycycline, imipenem, and ciprofloxacin.

The antibiotic sensitivity profile would occasionally change over time without major explanations.

**Data Analysis**

Descriptive analysis of continuous variables was done calculating mean, standard deviation, median, quartiles, and range, and by plotting the data. Survival analysis was performed plotting Kaplan-Meier (20) curves and comparing the distributions by means of the log-rank test. Status by sex 90 d after transplant was analyzed with a chi-square statistic. Statistical analysis was done using SAS software, version 6.12 (SAS Institute, Cary, NC). Statistical significance was defined as p < 0.05. All tests were two-tailed.

**RESULTS**

**Demographics**

Between March 1988 and September 1996, 56 transplant procedures were performed in 53 recipients. There were three re-transplant procedures: (1) double lung transplantation in a patient who developed BO 1 yr after his first transplant; (2) single lung transplantation in a patient who developed a severe airway stricture 7 mo after the first transplant; (3) double lung transplantation in a patient who developed BO 4 yr after the first procedure. Before surgery, 28 of the 53 recipients were infected with *B. cepacia*. The median age of the *B. cepacia* positive and *B. cepacia* negative groups was 28.4 ± 6.6 (range 18 to 39) and 30.8 ± 8.0 (range 22 to 46) yr, respectively (p = 0.35). In the *B. cepacia* positive group there were six women and 22 men versus 12 women and 13 men in the *B. cepacia* negative group (p < 0.005).

**Infection Post-transplant**

Of the 28 patients who were *B. cepacia* positive pretransplant, 25 were positive post-transplant. Time of isolation of *B. cepacia* post-transplantation is illustrated in Table 2. None of the

TABLE 1

MAINTENANCE IMMUNOSUPPRESSION PROTOCOL

	Months				
	1-3	3-6	6-9	9-12	> 12
Cyclosporine, ng/ml	250-350	250-350	200-250	200-250	200-250
Azathioprine, mg/kg/d	1-1.5	1-1.5	1-1.5	1-1.5	1-1.5
Prednisone, mg/d	20	15	15/10*	15/5*	15/0*

\* Represents alternate day dosing.

TABLE 2

TIME OF ISOLATION OF *B. cepacia* POST-TRANSPLANTATION

Time Post-transplant	Patients
First month	19
Second month	6
Total	25

25 patients who were *B. cepacia* negative pretransplant have had positive sputum or BAL specimens for *B. cepacia* post-transplant. The median follow-up for the complete group of patients as of August 1997 was 34.2 mo (range 0.3 to 113.7 mo). Median follow-up for the *B. cepacia* negative group was 42.6 mo (range 0.3 to 113.7 mo) and for the *B. cepacia* positive group 17.5 mo (range 0.3 to 90.2).

### Outcome

Nineteen of the 53 CF recipients (36%) have died. Fifteen of the deaths have occurred in the *B. cepacia* positive group and four in the *B. cepacia* negative group. Of the 15 patients who died in the *B. cepacia* positive group, *B. cepacia* was primarily responsible or involved in the death of 14; the other recipient died from metastatic melanoma. Nine of the 15 deaths (60%) occurred during the first 3 mo post-transplantation. The causes of death in the *B. cepacia* negative group were: BO, sepsis and cyclosporine toxicity, hyperacute rejection, and colon cancer. Whereas the majority of deaths in the *B. cepacia* positive group occurred shortly after transplantation, only two deaths occurred in the *B. cepacia* negative group within the first 3 mo post-transplant (hyperacute rejection in a single lung retransplant recipient who died immediately after the operation and another who died with sepsis and cyclosporine toxicity 10 d after transplant).

Survival is illustrated in Figure 1. The 1, 2, and 3-yr survival is 67, 49, and 45% in the *B. cepacia* positive group, compared with 96, 92, and 86% in the *B. cepacia* negative group. Comparison of the curves yielded a clinically and statistically significant difference ( $p < 0.01$ ). Excluding those who died within the first 3 mo, the 1-, 2-, and 3-yr survival is 100, 73, and 67%, respectively, for the *B. cepacia* positive group.

### Clinical Presentations of Complications Associated with *B. cepacia* Infection after Transplantation

The recipients have been divided into three groups based on the type of complication and the time when the complication appeared:

1. *Early death.* During the first 3 mo post-transplantation, disease was generally manifest as progressive infiltrates on chest radiographs, with increasing alveolar-arterial oxygen gradients, sepsis, and death, despite multiple intravenous antibiotics. This pattern was responsible for the death of four recipients who died in the intensive care unit without ever being extubated

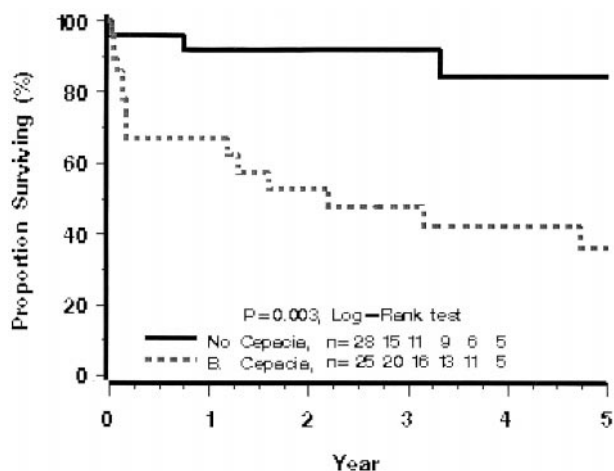


Figure 1. Kaplan-Meier survival curves of CF lung transplant recipients classified by *B. cepacia* infection status. The data show the number of subjects at each time point according to infection category.

post-transplantation (median survival post-transplantation was 27.5 d, range 8 to 60). Four others had the same course but while they continued to be hospitalized in the general transplant ward (median days post-transplantation 41, range 15 to 56). Another recipient was readmitted with pneumonia shortly after the initial hospital discharge for pneumonia with rapid progression to death 60 d after transplantation. One of the patients who died in the intensive care unit had concomitant CMV disease and another had an airway dehiscence.

2. *Late death.* Five patients died between 14 and 48 mo post-transplantation with *B. cepacia* infection associated with BO. Three of these patients developed abscesses due to *B. cepacia*; one had pneumonia and acute renal failure.

3. *Other pulmonary complications in survivors.* Of the 13 patients who survived, two had a localized abscess approximately 5 mo post-transplantation. Both patients had the abscesses resected. Both patients are well at 1 and 9 yr post-transplantation. One recipient developed an empyema from *B. cepacia*, which required an open surgical drainage procedure; this patient has survived 6 yr. One other recipient had pulmonary abscesses after developing BO. Treatment with a prolonged course of multiple antibiotics led to resolution of the abscesses.

### Bronchiolitis Obliterans Syndrome (BOS)

Defined according to the criteria published by Cooper and coworkers (21), BOS was present in seven of the patients who have died, five in the *B. cepacia* positive group (33% of those infected with *B. cepacia* who died) and two in the *B. cepacia* negative group (50% of those without cepacia who died). In those who continue to survive, 16 of 34 have evidence of BOS, six from the *B. cepacia* positive group (46% of the group) and 10 in the *B. cepacia* negative group (48% of the group). BOS grades are listed in Table 3.

### Autopsies

Eight of the nine patients who died during the early postoperative period had autopsies performed. The most common finding was the presence of widespread, bilateral pneumonia in seven with only one patient having a unilateral right pneumonia. Five patients also had multiple areas of lung necrosis and cavitation. Dehiscence of the bronchial anastomosis was present in two recipients. Four of the five patients who died beyond 3 mo had autopsies. Two transplant recipients had localized abscesses and two had diffuse bilateral infiltrates without cavitations. Pathologic examination of all five revealed extensive BO.

TABLE 3  
BOS IN CF RECIPIENTS WITH OR WITHOUT  
INFECTION WITH *B. cepacia*

B. cepacia (+) (n = 28)		BOS Stage	B. cepacia (-) (n = 25)	
Alive (n = 6)	Dead (n = 5)		Alive (n = 10)	Dead (n = 2)
3	1	3b	3	1
1	3	3a	1	—
1	—	2b	1	—
—	1	2a	1	—
—	—	1b	—	—
—	—	1a	1	1
—	—	0b	2	—
1	—	0a	1	—

### Results of Revised Immunosuppression and Antimicrobial Protocol

Five patients have received the new post-transplant antibiotic and immunosuppressive protocol. All of these recipients survived beyond the first year post-transplant (mean survival 17 mo, range 12 to 17).

One of the five recipients developed a severe respiratory tract infection with a concomitant chest wall abscess caused by *B. cepacia* 9 mo after transplantation. The patient had positive BAL cultures for *B. cepacia* early post-transplant. After recovering from the initial respiratory tract and chest wall infection, a second respiratory tract infection caused by *B. cepacia* occurred 16 mo after transplantation, after the development of BO. The patient died as a result of this *B. cepacia* pneumonia and BO. However, unlike many of the deaths associated with *B. cepacia*, the death occurred beyond 1 yr. As BO is extremely common after lung transplant, we cannot state whether the altered immunosuppression strategy was a contributing factor, although it is not unreasonable to presume that reduced immunosuppression would increase the likelihood of developing a process thought to be chronic rejection.

All five recipients had *B. cepacia* resistant to multiple antibiotics, including cephalosporins and aminoglycosides. *B. cepacia* has been isolated post-transplant in two patients. The aforementioned patient who died had positive cultures from sputum, BAL, and the abscess. The second patient developed a localized abscess, which revealed *B. cepacia* that was resistant to multiple antibiotics. This abscess was resected 5 mo after transplantation. The other three patients have had negative sputum and BAL cultures for *B. cepacia* and remain clinically stable.

### DISCUSSION

The last decade has been characterized by several significant advances in our understanding and treatment of CF. Perhaps the most important has been the discovery of the CF transmembrane conductance regulator gene which will hopefully lead to a cure (22, 23). As well, novel medical therapies such as recombinant deoxyribonuclease (DNase) have been developed (24). Nevertheless, the most important advance in clinical care in the last decade has been lung transplantation, a procedure that in some patients has the potential to improve quality and quantity of life dramatically (24–26).

Despite research advances made to date, people with CF continue to die from progressive bronchiectasis and chronic respiratory failure. The organisms most commonly cultured from the airways are *S. aureus* and *P. aeruginosa*. *B. cepacia* is much less common and is present in 3.2% of the American CF population (27) and 15% of the Canadian CF population (Canadian CF Foundation Patient Data Registry).

The reason for this plant pathogen (intrinsically resistant to multiple antibiotics) to cause infection in CF is still unknown. Over the past decade advances in genotyping techniques and the formation of the International *Burkholderia cepacia* Working Group have facilitated collaborative studies and a better understanding of this organism.

Genotypic and phenotypic analysis of *B. cepacia* strains has shown considerable heterogeneity. Recently, the term “genomovar” has been used to describe phenotypically similar but genotypically distinct groups of strains (28, 29). Vandamme and colleagues have proposed that *B. cepacia* be classified into at least distinct genomovars that make up the *B. cepacia* complex. The majority of CF isolates belong to Genomovars III and II. The clinical significance and pathogenic potential of these different genomovars are not yet known.

There is good evidence to suggest person-to-person spread of *B. cepacia*. Some strains are highly transmissible and can rapidly spread throughout a clinic and in fact across the Atlantic (30, 31). In contrast, in some centers there are multiple different strains of *B. cepacia*, suggesting low transmissibility (32). Presence of giant cable pili on the surface of some strains of *B. cepacia* may result in increased adherence to airway epithelial cells, and this may play a role in transmissibility of these bacteria from patient to patient (33). Implementation of infection control policies segregating “cepacia positive” and “cepacia negative” patients has reduced new acquisitions of *B. cepacia*; and until more is known about transmission factors, this measure is critically important to minimize spread in patients both pretransplant and post-transplant.

In addition, there is a great variability in the outcome of infection with *B. cepacia* in patients with CF. Some patients have no change in clinical course many years after acquisition of *B. cepacia* whereas others deteriorate at a more rapid rate and a small proportion will have a rapid, fatal deterioration over weeks (cepacia syndrome) (5, 8). In Toronto, virtually all patients with *B. cepacia* have the same strain, the ET 12 strain of Genomovar III; all these clinical patterns have been seen in the pretransplant population. To date, there has been no clear marker or predictor of virulence.

In a study of 13 patients, Lipuma and coworkers (28) documented that different centers had different ribotypes but there was no description of whether the ribotypes were associated with differing degrees of virulence. High transmissibility was noted. Variability in the course of lung disease was documented, with some individuals exhibiting a progressive rapid deterioration and some with gradual progression allowing prolonged survival. Similarly, data from Johnson (31) suggest that some clones predominate in wide geographic areas and that some strains may have a higher prevalence and associated mortality. Further studies are required to clarify the aggressiveness of certain ribotypes in order to identify those patients at higher risk of developing more severe infections and rapid deterioration in functional status.

Certain characteristics such as moderate to advanced disease, older age group, and male sex are associated with a higher incidence of infection (10). In our group of transplant recipients there were 22 men and six women who were infected with *B. cepacia* before transplantation. Although the reason for the male predominance is unclear, one possible explanation could be that women predisposed to developing *B. cepacia* infection died earlier and did not make it to the lung transplant assessment.

With increasing experience in transplanting patients with CF, it became evident that those who were infected with *B. cepacia* had a different outcome from those who were not. Our initial experience with 17 patients who received double lung transplantation for CF (16) reveals actuarial survival rates at 3, 6, and 12 mo of 68, 58, and 58%, respectively. Although survival has increased according to the more recent data, mortality associated with *B. cepacia* continues to exceed the non-*B. cepacia* host. Snell and coworkers (17) reported a 47% mortality among 22 CF lung transplant recipients who were infected with *B. cepacia*. Reports from other lung transplant programs also suggest a high mortality in those harboring *B. cepacia*. In a series of 44 patients Egan and coworkers (14) reported two deaths early post-transplant due to *B. cepacia*, but did not find a higher overall mortality in those infected with *B. cepacia*. A recent report from North Carolina (15) found that overall mortality (3 of 8, 38%) attributable to pretransplant infection with *B. cepacia* was comparable with the earlier report from Toronto; however, the number of cases was too small to draw broad conclusions. In addition, the investigators

also noted that panresistant *B. cepacia* infection was associated with a lower 1-yr survival (50% versus 90%) and higher mortality attributable to *B. cepacia* (50% versus 0%) compared with panresistant *P. aeruginosa* infection.

The Stanford group has suggested that maxillary sinus antrostomy and repeated sinus lavage are beneficial to patients who undergo thoracic transplantation due to CF (34); however, there are inadequate data at this time to suggest that such a strategy would be of benefit to patients infected with *B. cepacia*. We have been unable to detect a discernible difference in outcome after a limited attempt at prophylactic sinus procedures in patients with CF and therefore do not perform sinus surgery unless clinically indicated.

Use of antibiotics postoperatively for as long as 2 to 3 wk appears to be a fairly uniform practice for CF recipients of lung allografts. The prescribed antibiotics are chosen to ensure adequate activity against *P. aeruginosa* and most often include an aminoglycoside and a third-generation cephalosporin (35–37). Despite the standard use of tobramycin and ceftazidime in patients with CF in our program, overwhelming *B. cepacia* infection was frequent. Given the disappointing results of the previous protocols, we sought an aggressive protocol combining multiple antibiotics (tobramycin [intravenous and inhaled] ceftazidime, chloramphenicol, and TMS) and a reduced level of immune suppression. Chloramphenicol has been available for over 50 yr but has fallen out of favor owing to rare but serious reports of aplastic anemia (38, 39). To date, we have used this protocol with five patients, all of whom have survived beyond 1 yr. One of the five patients died 17 mo post-transplantation as a result of *B. cepacia* infection and severe chronic rejection. The other four patients have survived beyond 1 yr (mean 17.2 mo, range 12 to 24). Although the numbers are small, our results are encouraging.

Synergy test is now more common and can offer a more sensible way to treat infected patients. However, Burns and Saiman (40) found no two-drug synergistic combinations in 57% of 652 *B. cepacia* isolates tested from 330 patients with CF. If this is a reproducible finding, synergy testing will have limited utility in those with *B. cepacia*. In our program we do not have enough experience yet to either confirm or refute their findings.

It is reasonable to ask whether transplantation should continue to be performed in patients with CF colonized with *B. cepacia*. The issue of who should and who should not be transplanted remains controversial and unresolved. The use of length of survival is not the only standard that should be considered (41). What of quality of life? What is the trade-off between quality and quantity? There are several reasons why we continue to transplant this population. Virtually 50% of the CF population in the Toronto program are colonized with this organism; we would therefore be excluding many young people without other options for prolonged survival. There are clearly patients with *B. cepacia* who have a fairly unremarkable post-transplant course and have a prolonged survival; denial of transplant to such individuals would be tragic. We are conducting investigations to try to identify those patients. Finally, we believe improvements in immunosuppression and antimicrobial protocols will lead to improvements in survival for those colonized with *B. cepacia*.

Once established in the airways, *B. cepacia* is extremely difficult to treat and is associated with excess morbidity and mortality. Several publications (10, 17, 28, 32, 42, 43) have emphasized the importance of decreasing the possibility of transmission as a way to decrease infection and subsequent morbidity. Even if this is successful, there is a cohort of patients infected with *B. cepacia* for whom the only option for long-

term survival is transplantation. Although our experience has demonstrated a reduced survival compared with other populations with advanced lung disease, our improved results, particularly with a redesigned post-transplant medication protocol, suggest that long-term survival is possible. Furthermore, we have found that if a patient with *B. cepacia* survives beyond 3 mo, results of transplantation are reasonably acceptable. It therefore behooves health care professionals to continue to study this organism and develop new ways to prevent infection or techniques to allow the host to survive after lung transplantation despite *B. cepacia*.

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