

# Survival After Lung Transplantation of Cystic Fibrosis Patients Infected with *Burkholderia cepacia* Complex

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**Within the *Burkholderia cepacia* complex (Bcc), *B. cenocepacia* portends increased mortality compared with other species. We investigated the impact of Bcc infection on mortality and re-infection following lung transplant (LT). Species designation for isolates from Bcc-infected patients was determined using 16S rDNA and *recA* gene analyses. Of 75 cystic fibrosis patients undergoing LT from September 1992 to August 2002, 59 had no Bcc and 16 had Bcc (including 7 *B. cenocepacia*) isolated in the year before LT. Of the latter, 87.5% had Bcc recovered after transplantation, and all retained their pretransplant strains. Survival was 97%, 92%, 76% and 63% for noninfected patients; 89%, 89%, 67% and 56% for patients infected with Bcc species other than *B. cenocepacia*; and 71%, 29%, 29% and 29% for patients with *B. cenocepacia* ( $p = 0.014$ ) at 1 month, 1 year, 3 years and 5 years, respectively. Patients infected with *B. cenocepacia* before transplant were six times more likely to die within 1 year of transplant than those infected with other Bcc species ( $p = 0.04$ ) and eight times than noninfected patients ( $p < 0.00005$ ). Following LT, infection with Bcc species other than *B. cenocepacia* does not significantly impact 5-year survival whereas infection with *B. cenocepacia* pretransplant is associated with decreased survival.**

**Key words:** Bacterial infection, lung transplantation, transplant infectious diseases, transplant outcome

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## Introduction

The *Burkholderia cepacia* complex (Bcc) consists of at least nine phenotypically similar but genotypically distinct species (previously referred to as genomovars) of non-fermenting, gram-negative rods. These include *B. cepacia* (genomovar I), *B. multivorans* (genomovar II), *B. cenocepacia* (genomovar III), *B. stabilis* (genomovar IV), *B. vietnamiensis* (genomovar V), *B. dolosa* (genomovar VI), *B. ambifaria* (genomovar VII), *B. anthina* (genomovar VIII) and *B. pyrrocinia* (genomovar IX) (1–4). Colonization and subsequent infection in cystic fibrosis (CF) patients with Bcc has been associated with poor outcomes, including accelerated decline in pulmonary function and fatal disease (5–7). Organisms belonging to each Bcc species have been recovered from patients with CF; however, the majority of clinical isolates are *B. multivorans* and *B. cenocepacia* (8–11). Furthermore, isolates associated with increased morbidity and mortality may cluster within the *B. cenocepacia* species (12,13). Several epidemiologic studies have shown that some strains of Bcc are highly transmissible between patients, although a few studies have shown no evidence of transmission (14). Based on these observations, it seems that certain Bcc species and / or strains may be more transmissible than others, and likewise, some may be more virulent.

Lung transplantation is a therapeutic option for an increasing number of persons affected by CF. Patients with CF who are infected with Bcc present a particular dilemma for lung transplantation. Aris et al. reported in a retrospective review of patients undergoing lung transplantation that mortality was significantly increased in patients infected with Bcc (15). Snell and colleagues had previously reported a similar finding of high mortality (47%) among patients infected with Bcc prior to transplant (16). In a series of 53 CF patients transplanted in Toronto between 1988 and 1996, 1-year survival was 67% in the Bcc-infected patients versus 92% among noninfected patients. A majority (9/15, 60%) of deaths in the Bcc cohort was in the first 3 months following transplantation and was characterized by progressive acute respiratory distress syndrome and sepsis (17). Consequently, many centers consider infection with Bcc a contraindication to transplantation. Other centers, however, continued to transplant these patients. In support of this practice, Kanj et al. reported the early experience at Duke University Medical Center (DUMC), where infection with *Burkholderia* species did not seem to predict a worse

outcome (18). Likewise, Flume and Egan reported lower mortalities associated with Bcc infection than previously described (19,20). More recent studies suggest that within the Bcc, *B. cenocepacia* is associated with increased mortality rates compared with other species (21–23). For example, of 121 CF patients transplanted at the University of North Carolina, excessive early mortality was noted in Bcc-infected patients, with a 6-month mortality of 33% compared with 12% in noninfected patients. All early deaths occurred in patients infected with *B. cenocepacia* (22).

DUMC is a CF treatment and lung transplantation center. The first lung transplant (LT) procedure at DUMC was performed in 1992, and until 2002, patients infected with Bcc including *B. cenocepacia* were regularly transplanted at DUMC. This retrospective investigation was performed to assess the impact of Bcc infection on mortality and re-infection following lung transplantation in patients with CF.

## Materials and Methods

Following Duke University Health System Institutional Review Board approval, the DUMC LT database was queried for all patients undergoing transplantation between September 1992 and August 2002 and consecutive patients with CF as the underlying disease leading to LT were thus identified and included in the study. Using a standardized case report form, clinical data were collected from paper charts and computerized records. Recipient age at time of transplant, donor age, mechanical ventilation for recipient at time of LT, graft ischemia time, mismatches in human leukocyte antigens, donor/recipient CMV serostatus and date of death and/or lung retransplantation were recorded. Complete 5 year follow-up was available on each patient. Prior to transplant, respiratory samples were submitted for bacterial culture that included Bcc selective media (OFFBL Agar, Remel, Lenexa, KS), as part of routine work-up for transplantation and for management of CF including acute exacerbations. Patients underwent surveillance bronchoscopy with bronchoalveolar lavage (BAL) bacterial culture at 1, 3, 6, 9 and 12 months posttransplant or at any point if clinical indications developed (e.g. decrease in lung function, fever, new infiltrate on chest radiograph). Sputum samples for diagnostic purposes were also submitted from patients with clinical symptoms who were able to produce sputum.

Bcc were defined as multidrug resistant if they were intermediate or resistant to at least one agent in each of three classes of antibiotics including the  $\beta$ -lactams, sulfonamides and fluoroquinolones. Organisms were defined as panresistant if they were resistant to all drugs tested. LT recipients infected with Bcc generally received four systemic antibiotics known to be effective against the patient's Bcc isolate based on susceptibility testing for at least 3 weeks. For isolates found to be multidrug or panresistant, antibiotics were selected based on two-drug combination synergy testing performed by Dr. Lisa Saiman's laboratory, Columbia University. All CF patients transplanted at DUMC also received aerosolized colistin and tobramycin for 3 months following transplant as routine prophylaxis, regardless of infecting flora. Patients received triple drug immunosuppression with cyclosporine (prior to 1999) or tacrolimus (after 1999), azathioprine and corticosteroids. Induction with an interleukin-2 receptor agent (basiliximab) was also administered beginning in 1999. Details of the surgical procedure, posttransplant management and follow-up have been previously described (24,25).

The DUMC Clinical Microbiology Laboratory (CML) maintains a frozen sample ( $-70^{\circ}\text{C}$ ) of all bacterial isolates obtained from blood as well as isolates obtained from respiratory specimens of persons with CF. Gram-negative,

oxidase-positive, nonfermenting rods were preliminarily identified as Bcc by cell wall analysis with gas-liquid chromatography (MIDI System; Microbial ID, Newark, DE). The CML database was queried for all cultures submitted from this cohort of patients to identify cultures that grew Bcc. Isolates were categorized based on clinical specimen type and date of specimen collection and those isolates available were recovered from frozen stocks and further analyzed at the *Burkholderia cepacia* Research Laboratory and Repository, University of Michigan. Isolates were confirmed as members of the genus *Burkholderia*, and species designation within the Bcc was determined utilizing 16S rDNA and *recA* species-specific polymerase chain reaction (PCR) and *recA* restriction fragment length polymorphism (RFLP) analyses (26,27). Box PCR typing was performed, as previously described, on isolates to determine strain relatedness (28). For the purposes of this study, distinct strain types were assigned different alphabetic designations.

## Statistical method

Statistical analyses were performed using Analyse-It software (Analyse-It Software Ltd, Leeds, UK) for Microsoft Excel and JMP Statistical Discovery Program (version 6.0, SAS Institute, Cary, NC) and a type-I error rate of 0.05. Descriptive statistics performed on the data set included measures of central tendency and spread for continuous variables and percentages and frequencies for categorical variables. Infection status within 1 year prior to transplant was divided into three following categories for analysis purpose: patients without Bcc isolated were considered 'noninfected', patients harboring a species of Bcc other than *B. cenocepacia* were considered 'other Bcc species' and patients harboring *B. cenocepacia* were considered '*B. cenocepacia*'. Subjects for whom Bcc was isolated within 1 year of LT but for whom no isolate was available for further speciation were excluded from analysis. Subjects for whom Bcc was not isolated prior to transplant but was isolated after transplant were considered 'noninfected'. Three way comparisons between the groups based on infection status were performed using one-way ANOVA for continuous variables including the Kruskal-Wallis test for nonparametric sensitivity analyses and Tukey's method for multiple comparisons. The chi-square test was used for categorical variables. Survival curves were calculated with the Kaplan-Meier method and compared using the log-rank test. Survival status was divided into two categories—'alive' or 'dead or retransplanted' at 1 year post LT. Logistic regression analyses were performed to investigate the relationship of infection status, recipient age at time of transplant, donor age, mechanical ventilation for recipient at time of LT, graft ischemia time, mismatches in human leukocyte antigens, receipt of trimethoprim/sulfamethoxazole following transplant and donor/recipient CMV serostatus on survival status 1 year post LT. The sample size was insufficient for multivariable modeling. Missing data points were not replaced.

## Results

Seventy-six consecutive CF patients underwent LT at DUMC between September 1992 and August 2002. During the year before transplant, 59 (77.6%) patients were 'noninfected', 9 (12.0%) harbored 'other Bcc species', including *B. multivorans* (7 patients, 9.2%) and *B. vietnamiensis* (2 patients, 2.6%), and 7 (9.2%) harbored *B. cenocepacia*. One patient was excluded because her pretransplant isolate was not available for evaluation. Two patients had *B. cenocepacia* isolated post transplant, including one patient with both *B. cenocepacia* and *B. multivorans*, but no Bcc isolated pretransplant. These patients were included in the 'noninfected' group for primary analysis. Four patients required a second transplant.

Patient characteristics at the time of lung transplantation are included in Table 1. The average patient age was 27.7 years (SD 8.5, range 11 to 53). Gender, CMV serostatus, mean age at time of transplant, mean donor age, median graft ischemic time and number of HLA mismatches did not differ significantly between the three groups. All patients were Caucasian and only one, who was infected with *B. cenocepacia*, was of Hispanic/Latino ethnicity. Six (86%) patients had multidrug resistant *B. cenocepacia*, of which three (43%) had panresistant *B. cenocepacia*. Seven (78%) patients infected with 'other Bcc species' had multidrug resistant organisms recovered, of which five (56%) were considered panresistant. Similarly, five (71%) and seven (78%) patients in the *B. cenocepacia* and 'other Bcc species' groups, respectively, were colonized with other potential pathogens including *Staphylococcus aureus* or another gram-negative rod. These differences were not significant.

Of 16 CF patients infected with Bcc prior to transplant, all but two had Bcc recovered from respiratory cultures post transplant. These two patients had 9 and 4 BAL samples cultured post transplant, respectively. All patients infected with Bcc prior to transplant and who had Bcc recovered from clinical specimens post transplant retained their pre-transplant strains (Table 2).

Within 1 year of LT, 11 patients died including 8.5% (5/59) of patients in the 'noninfected' group, 11.1% (1/9) of patients in the 'other Bcc species' group and 71.4% (5/7) of patients in the '*B. cenocepacia*' group. Infection status was significantly associated with 1-year survival ( $p < 0.0001$ ). Survival

estimates for 'noninfected' patients were 97%, 92%, 76% and 63%, at 1 month, 1 year, 3 years and 5 years, respectively, compared with 89%, 89%, 67% and 56% in patients with 'other Bcc species' and 71%, 29%, 29% and 29% for patients with '*B. cenocepacia*' ( $p = 0.0142$ , Figure 1). Survival estimates were worse for patients with '*B. cenocepacia*' when compared with all other patients combined as a single group ( $p < 0.0037$ ). In fact, patients infected with *B. cenocepacia* prior to transplant were eight times more likely to die within 1 year of transplant than those not infected (RR = 8.43, 95% CI 3.23–22.03,  $p < 0.00005$ ) and six times more likely to die within 1 year of transplant than those infected with 'other Bcc species' prior to transplant (RR = 6.43, 95% CI, 0.95–43.26,  $p = 0.04$ ).

Gender, recipient age, donor age, mechanical ventilation at time of transplant, graft ischemic time, mismatches in human leukocyte antigens, CMV serostatus, receipt of trimethoprim/sulfamethoxazole following transplant and pre LT infection with 'other Bcc species' had no association with 1-year survival.

**Discussion**

Several studies have established that for CF patients, infection with Bcc is an independent predictor of early death and accelerated decline in pulmonary function. Thus, many patients infected with Bcc seek lung transplantation as a life-extending option when their respiratory status begins to decline. This investigation into the impact of Bcc

**Table 1:** Patient characteristics at the time of lung transplantation by pre-transplant *Burkholderia cepacia* complex (Bcc) infection status

Variable	Infection status <sup>1</sup>		
	<i>B. cenocepacia</i> N = 7	Other Bcc species <sup>2</sup> N = 9	Noninfected N = 59
Recipient age in years (Median, IQR)	24 (21–33)	28 (27–33)	27 (22–33)
Male N (%)	3 (42.9)	4 (44.4)	26 (44.1)
Mechanical ventilation at time of transplant N (%)	0	0	6 (10.2)
CMV risk status <sup>3</sup> N (%)			
High	2 (28.6)	3 (33.3)	19 (32.2)
Intermediate	4 (57.1)	5 (55.6)	22 (37.3)
Low	1 (14.3)	1 (11.1)	18 (30.5)
Donor age in years (Median, IQR)	22 (17–28)	17 (15–26)	25 (15–40)
No. HLA mismatches (Median, IQR)	5 (4–5.5)	4 (4–5)	5 (4–5.25)
Graft ischemic time (h) (Median, IQR)	634 (601.5–713.5)	652 (525–706)	636 (547.5–728.8)

<sup>1</sup> infection status within 1 year prior to lung transplant.

<sup>2</sup> Bcc species other than *B. cenocepacia*.

<sup>3</sup> High risk, recipient seronegative and donor seropositive; Intermediate risk, seropositive recipient; Low risk, seronegative recipient and donor.

SD = standard deviation; CMV = cytomegalovirus; HLA = human leukocyte antigens; IQR = interquartile range.

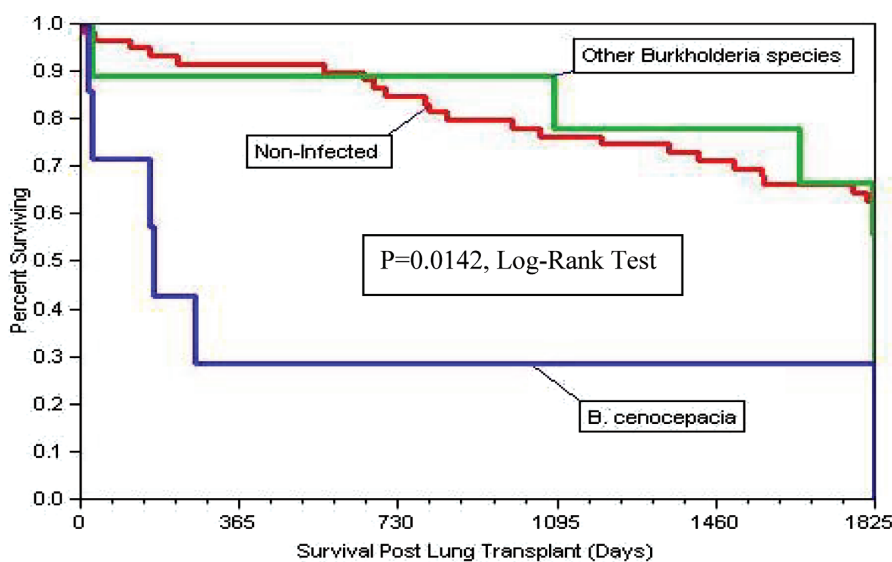
**Table 2:** *Burkholderia cepacia* complex species and strain type infecting CF patients prior to and 5 years after lung transplantation

Patient	<i>Burkholderia</i> species	Strain type <sup>1</sup>		Survival posttransplant (Days)	Cause of death
		Pretransplant	Posttransplant		
1	<i>B. cenocepacia</i>	AA	AA	29	<i>Burkholderia</i> pneumonia
2	<i>B. cenocepacia</i>	I	No Bcc isolated	16	Anoxic brain injury
3	<i>B. cenocepacia</i>	W	W	170	<i>Burkholderia</i> sepsis
4	<i>B. cenocepacia</i>	I	I	>1825	Alive
5	<i>B. cenocepacia</i>	X	No Bcc isolated	266	Respiratory failure/Rejection
6	<i>B. cenocepacia</i>	AF	AF	>1825	Alive
7	<i>B. cenocepacia</i>	S	S	158	<i>Burkholderia</i> sepsis
8	<i>B. cenocepacia</i>	No Bcc isolated	B and A	223	Respiratory failure
	<i>B. multivorans</i>		C		
9	<i>B. cenocepacia</i>	No Bcc isolated	B	>1825	Alive
10	<i>B. multivorans</i>	U	U	1820	<i>Burkholderia</i> sepsis
11	<i>B. multivorans</i>	AI	AI	1086	Cancer
12	<i>B. multivorans</i>	T	T	>1825	Alive
13	<i>B. multivorans</i>	AJ	AJ	>1825	Alive
14	<i>B. multivorans</i>	AH	Bcc isolate not saved	>1825	Alive
15	<i>B. multivorans</i>	L	L	>1825	Alive
16	<i>B. multivorans</i>	AC	AC	1651	Bronchiolitis obliterans syndrome
17	<i>B. vietnamiensis</i>	N	N	26	Diffuse alveolar damage
18	<i>B. vietnamiensis</i>	AB	AB	>1825	Alive

<sup>1</sup> Each unique alphabet designation represents a distinct strain type, as determined by Box PCR typing.

respiratory infection in CF patients on re-infection rates and survival following lung transplantation offers additional and important insight for the management of these patients. Contrary to the early data from our institution, infection with Bcc prior to transplant, and more specifically, infection with *B. cenocepacia*, significantly impacts survival. Mortality was significantly worse for those CF patients infected with *B. cenocepacia* compared with noninfected CF patients and CF patients infected with Bcc species other than *B. cenocepacia*. Furthermore, the negative effect was most dramatic during the first year following the transplant pro-

cedure. Per Table 2, over half of the patients infected with *B. cenocepacia* in our cohort were dead within the first 6 months following the transplant procedure, and *Burkholderia* pneumonia or sepsis was considered the cause of death for all but one. In contrast, *Burkholderia* infection was considered the cause of death for only one patient infected with other *Burkholderia* species and as a contributor to the cause of death for only one patient not infected with Bcc prior to transplant (acquired following the transplant procedure), during the 5-year follow-up. Although this study is clearly limited by the small number of patients with



**Figure 1:** Five-year survival for cystic fibrosis patients following lung transplant based on pretransplant *Burkholderia cepacia* complex infection status. Infection status within 1 year prior to transplant was divided into three categories for analysis purposes as follows: patients without Bcc isolated were considered 'noninfected', patients harboring a species of Bcc other than *B. cenocepacia* were considered 'other *Burkholderia* species' and patients harboring *B. cenocepacia* were considered '*B. cenocepacia*'.

*B. cenocepacia* in the cohort and the retrospective design, the results are striking and are consistent with reports from other LT centers (21,22). For example, De Soyza and coworkers in Newcastle-Upon-Tyne, UK, reported early deaths following lung transplantation for 4 of 4 patients infected with *B. cenocepacia* strain ET12, which is common in eastern Canada and the UK and has been associated with poor outcome (29), but no deaths among 5 patients infected with other Bcc species (mean follow-up 1.9 years) (21). Aris and colleagues at the University of North Carolina reported the death of 5 of 12 patients infected with *B. cenocepacia* (none of which were infected with strain ET12) compared with no deaths in the 8 patients infected with other Bcc species (mean follow-up 1.5 years) (22). Our data confirm the early mortality associated with *B. cenocepacia* infection and offer important new insights into the long-term survival of patients infected with other Bcc species. In fact, 5-year survival for patients infected with Bcc other than *B. cenocepacia* did not significantly differ from that of noninfected CF patients and exceeds that of other groups considered at high-risk following lung transplantation, such as those transplanted due to idiopathic pulmonary fibrosis or primary pulmonary hypertension ([www.ustransplant.org/annual\\_reports/current/survival\\_rates.htm](http://www.ustransplant.org/annual_reports/current/survival_rates.htm)). As with the study by Aris et al., the heterogeneity of *B. cenocepacia* strains recovered in our cohort also indicates that increased virulence is not limited to a single strain type (e.g. *B. cenocepacia* strain ET12). However, whether these observations can be extrapolated to conclude that 'all' strains of *B. cenocepacia* have the same capacity for poor outcome in LT recipients is not clear.

Consistent with previous reports from other institutions, CF patients in our cohort were almost uniformly re-infected with their pretransplant infecting strain of Bcc following the LT procedure (14). All transplant recipients in this cohort received bilateral LTs, thereby eliminating a native lung as a potential source of re-infection. All transplanted grafts were cultured before implantation and none grew Bcc, effectively ruling out the transplanted lungs as the source of infection. The sinuses are another potential and highly likely reservoir for autologous infection of the new lungs. Whether prophylactic sinus procedures in CF patients prior to transplant would decrease the rate of pulmonary re-infection would need to be studied. The majority of patients in our cohort did not undergo sinus surgery within 1 year prior to transplant; only one patient colonized with '*B. cenocepacia*' and one patient colonized with 'other Bcc species' underwent sinus surgery. Another important potential source for re-infection is the patient's caregivers; although if this were the case, one would expect re-infection with a strain different from their pretransplant clone in at least some of the patients. With that said, our data do highlight the importance of stringent infection control practices to decrease nosocomial transmission of these pathogens. Two of our patients had no *B. cenocepacia* recovered before transplantation, but did develop infection with *B. cenocepacia* post transplant. One of these patients had *B. ceno-*

*cepacia* first recovered from BAL collected 70 days post transplant although 5 total respiratory samples collected throughout the year preceding transplant and the first 30 BALs collected post transplant did not grow a Bcc species. Strain typing revealed this and subsequent *B. cenocepacia* strains (B and A) recovered from this patient to be the two strains identified during an outbreak of *B. cenocepacia* bloodstream infections at our institution between August 1997 and April 2001 (13). This patient also had *B. multivorans* recovered for the first time from BAL collected 85 days post transplant. Interestingly, this patient was never discharged following transplant, resulting in a 7-month hospitalization. The second patient had *B. cenocepacia* recovered from respiratory samples 2 months following transplant. Box PCR typing revealed this isolate to also be one of the *B. cenocepacia* institutional outbreak strains (B). Given the enhanced capacity for interpatient spread and associated poor outcome, our center instituted strict infection control measures, including gowning and gloving upon entering the room of and handwashing after contact with all Bcc-infected patients. The frequency of Bcc recovery within the institution rapidly decreased after these interventions. Accordingly, in addition to adherence to routine infection control practices for all patients undergoing lung transplantation, we strongly recommend placing any patient infected with *B. cenocepacia* under strict isolation precautions (13).

Due to the excessive mortality seen among patients infected with *B. cenocepacia*, the LT community is beginning to re-consider lung transplantation as an option for patients infected with this species. Available data support screening of all CF patients for Bcc and excluding those infected with *B. cenocepacia* from transplantation. Active research continues regarding pathogenesis and epidemiology of Bcc among CF patients. Currently, International Society for Heart and Lung Transplantation guidelines do not list *B. cenocepacia* infection as an absolute contraindication to lung transplantation; however, 'colonization with highly resistant or highly virulent bacteria' is included as a relative contraindication, thereby giving individual centers the ability to dictate practice (30). As with other reports, for CF patients infected with Bcc, antibiotic susceptibility patterns were not helpful in determining the likelihood of survival following lung transplantation (22). Although the optimization of antibiotic combinations and attenuation of immunosuppression for patients infected with Bcc have been offered as means of improving survival for these patients following transplant (17), careful selection of a 4-drug antibiotic regimen was not found to be beneficial in our group of patients with *B. cenocepacia*. Similarly, treatment with trimethoprim-sulfamethoxazole did not impact outcomes. Furthermore, given the very high rates of acute and chronic rejection after lung transplantation, it is unclear if a strategy of reduced immunosuppression would lead to any better long-term outcomes in this population due to the potential for a corresponding increase in rejection related deaths.

Cooperation between CF treatment and LT centers will hopefully provide new insights into virulence, transmissibility and treatment regimens for this unique and challenging pathogen. More specifically, further studies to identify which specific strains of *B. cenocepacia* may be more virulent, the mechanisms behind the virulence in such strains and investigations to tease out what host factors might influence progression of the infection in the CF population should be a priority. Until then, we recommend the careful screening of all CF patients for Bcc and excluding from LT those harboring *B. cenocepacia*, regardless of susceptibility profile.

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