

# Impact of *Burkholderia* Infection on Lung Transplantation in Cystic Fibrosis

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**Rationale:** Lung transplantation offers the only survival option for patients with cystic fibrosis (CF) with end-stage pulmonary disease. Infection with *Burkholderia* species is typically considered a contraindication to transplantation in CF. However, the risks posed by different *Burkholderia* species on transplantation outcomes are poorly defined.

**Objectives:** To quantify the risks of infection with *Burkholderia* species on survival before and after lung transplantation in patients with CF.

**Methods:** Multivariate Cox survival models assessed hazard ratios of infection with *Burkholderia* species in 1,026 lung transplant candidates and 528 lung transplant recipients. Lung allocation scores, incorporating *Burkholderia* infection status, were calculated for transplant candidates.

**Measurements and Main Results:** Transplant candidates infected with different *Burkholderia* species did not have statistically different mortality rates. Among transplant recipients infected with *B. cenocepacia*, only those infected with nonepidemic strains had significantly greater post-transplant mortality compared with uninfected patients (hazard ratio [HR], 2.52; 95% confidence interval [CI], 1.04–6.12;  $P = 0.04$ ). Hazards were similar between uninfected transplant recipients and those infected with *B. multivorans* (HR, 0.66; 95% CI, 0.27–1.56;  $P = 0.34$ ). Transplant recipients infected with *B. gladioli* had significantly greater post-transplant mortality than uninfected patients (HR, 2.23; 95% CI, 1.05–4.74;  $P = 0.04$ ). Once hazards for species/strain were included, lung allocation scores of *B. multivorans*-infected transplant candidates were comparable to uninfected candidate scores, whereas those of candidates infected with nonepidemic *B. cenocepacia* or *B. gladioli* were lower.

**Conclusions:** Post-transplant mortality among patients with CF infected with *Burkholderia* varies by infecting species. This variability should be taken into account in evaluating lung transplantation candidates.

**Keywords:** infection; lung allocation; transplant benefit; *Burkholderia*

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## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

*Burkholderia* infection is considered a contraindication to lung transplantation in cystic fibrosis. However, the risks posed by different *Burkholderia* species on outcomes after lung transplantation in cystic fibrosis are not well defined.

### What This Study Adds to the Field

This multivariate analysis shows that the risk of poor outcome after lung transplantation varies between *Burkholderia* species. These relative risks should be taken into account in evaluating lung transplantation candidates.

Therapeutic options for persons with cystic fibrosis (CF) with end-stage pulmonary disease are limited. Although some patients and their caregivers choose to pursue only aggressive medical therapy, other patients, if deemed eligible, may be offered the opportunity to undergo lung transplantation. Although CF is the third most common diagnosis among lung transplant recipients overall (behind idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease), it is the most common indication for lung transplantation in pediatric patients (1). Approximately 180 patients with CF underwent lung transplantation per year in the United States between 1996 and 2005 (1).

Estimates of clinical benefit after lung transplantation in patients with CF vary. Hosenpud and colleagues (2) used a retrospective time-dependent nonproportional hazard analysis to assess the risk of mortality after transplantation relative to that for patients on the transplant waiting list, and showed a significant benefit from transplantation in CF. Aurora and colleagues (3) used a proportional hazards model in a retrospective analysis to calculate a univariate hazard ratio (HR) showing that transplantation was significantly associated with survival after correction for several variables of prognostic significance in CF. In contrast, Liou and coworkers (4, 5) used a multivariable logistic regression survivorship model for CF to show that the majority of patients with CF have equivocal or negative survival effects from lung transplantation. More recently, Liou and coworkers used a proportional hazards model to again estimate that the majority of children with CF wait-listed for lung transplantation would actually have a significant risk of harm associated with the procedure (6). Thus, the role of lung transplantation in CF is controversial, but it is increasingly clear that selection of the most appropriate candidates for transplantation (i.e., those with the greatest likelihood of benefit) is critical.

To better allocate lungs for transplantation, the Scientific Registry of Transplant Recipients (SRTR) and the Organ Procurement and Transplantation Network (OPTN) developed a lung allocation score that estimates each patient's urgency and

potential transplant benefit based on probability models of lung wait-list and post-transplant survival (7). In May 2005, the OPTN implemented a national policy for lung allocation, prioritizing patients according to their lung allocation score. Data used in designing the lung allocation score, which incorporates variables shown in previous analyses to be important predictors of outcomes in lung transplantation in CF, were limited to those collected by the OPTN in its original development. The lung allocation scoring system is intended to be updated at frequent intervals, particularly as additional predictors are identified and merged with OPTN data on patient outcomes. For example, in March of 2007, PaCO<sub>2</sub> and measures of PaCO<sub>2</sub> change over a 6-month period were approved by the OPTN Board of Directors for inclusion in the lung allocation score based on such an analysis (8, 9). Additional predictors of mortality on the lung waiting list or after transplantation that can be validated within the OPTN patient population are of interest to national lung allocation policy makers.

Much of the morbidity and mortality associated with lung transplantation in CF are attributed to postoperative infectious complications. Infections with bacteria that exhibit broad-range antibiotic resistance have been found, not surprisingly, to be most problematic (10–14). Several studies during the 1990s identified infection with *Burkholderia cepacia*, in particular, to be associated with post-transplantation infectious complications and poor outcomes (14–20). Consequently, lung transplantation in persons infected with *Burkholderia* species is controversial (21, 22), and many transplant centers currently exclude such patients from transplantation waiting lists. However, early studies identifying *B. cepacia* as a risk in transplant recipients were performed before the realization that several distinct species constitute what is now referred to as the *B. cepacia* complex. These species, although very closely related phylogenetically and phenotypically, vary considerably in the frequency with which they cause infection in patients with CF. Together, *B. cenocepacia* and *B. multivorans* account for approximately 85% of *B. cepacia* complex infection in the United States (23). Emerging data further suggest that species within the *B. cepacia* complex also differ with respect to their virulence in this patient population (24). The risk associated with infection with *B. gladioli*, which, although not a member of the *B. cepacia* complex, also causes chronic respiratory tract infection in patients with CF, has not been assessed.

We undertook a retrospective multivariate survival analysis to assess the hazards of infection with different *Burkholderia* species in patients with CF being considered for or having received lung transplants. On the basis of the results of these analyses, we calculated a lung allocation score for wait-listed patients that includes infection status parameter estimates in the assessment of patient urgency and patient benefit.

## METHODS

### Patient Population and Control Subjects

This study was approved by the University of Michigan's Institutional Review Board for Human Subject Research, the Cystic Fibrosis Foundation (CFF) Patient Registry Committee, and the Health Resources and Services Administration's (U.S. Department of Health and Human Services) SRTR project officer.

**Lung waiting list cohort.** We identified all individuals from whom a sputum culture isolate was confirmed as *Burkholderia* by the *Burkholderia cepacia* Research Laboratory and Repository (BcRLR), and who received care in CFF-accredited care centers in the United States and were registered in the CFF Patient Registry (Bethesda, MD). Among this cohort of 1,541 *Burkholderia*-infected patients, 171 were registered as lung transplant candidates with the SRTR between January 1, 1997, and December 31, 2006, and were at least 12 years old at the time they

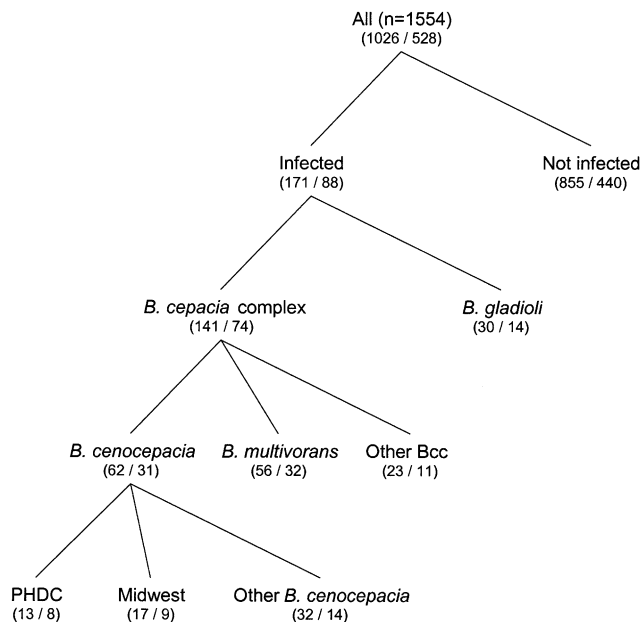
entered the lung transplant waiting list ("waiting list cases"). These 171 patients received care, over the course of this 10-year interval, in 209 CF care centers in the United States. There were an additional 2,105 patients with CF on the lung transplant waiting list who were at least 12 years old and not known to be infected with *Burkholderia* based on data from the CFF Patient Registry and the BcRLR ("waiting list control subjects"). To eliminate era effects due to differential distribution of listing dates between cases and control subjects, we selected five waiting list control subjects for each of the 171 *Burkholderia*-infected waiting list cases matched on year of listing for transplantation. Mortality data were supplemented as needed by using the Social Security Death Master File. The resulting 171 waiting list cases and 855 waiting list control subjects created a dataset of 1,026 "wait-listed candidates" for analysis.

**Transplant recipient cohort.** We identified 88 *Burkholderia*-infected patients with CF who were registered in the SRTR database as having received a lung transplant between January 1, 1997, and December 31, 2006, and who were at least 12 years old at the time of their transplant ("transplanted cases"). These 88 patients received lung transplantations in 23 transplant centers in the United States. There were an additional 1,426 patients with CF at least 12 years old who received a lung transplant during the same period but who were not known to be infected with *Burkholderia* before transplantation ("transplanted control subjects"). Five transplanted control subjects were matched to each transplanted case by year of transplant, creating a dataset of 528 "transplant recipients" (88 transplanted cases and 440 transplanted control subjects). Again, mortality data were supplemented by using the Social Security Death Master File.

A summary view of the groups analyzed in this study is shown in Figure 1.

### Microbiologic Analysis

Bacterial isolates recovered from CF respiratory specimens were confirmed as *Burkholderia* species by using 16S rDNA and *recA* species-specific polymerase chain reaction, and *recA* restriction fragment length polymorphism analyses as previously described (25, 26). Bacterial genotyping, using repetitive extragenic palindromic element polymerase chain reaction typing as previously described (27), was performed on isolates from all *Burkholderia*-infected patients to



**Figure 1.** Summary view of population studied. The numbers in parentheses for each group indicate the numbers of lung transplant candidates/recipients identified in the Scientific Registry of Transplant Recipients between January 1, 1997, and December 31, 2006. Other Bcc = *B. cepacia* complex species other than *B. cenocepacia* and *B. multivorans*.

determine strain type (and to identify previously reported epidemic *B. cenocepacia* strains, such as strain PHDC and the Midwest clone).

### Statistical Analysis

Multivariate Cox models were used to examine the associations between *Burkholderia* infection status and waiting list and post-transplant mortality in the context of the SRTR/OPTN lung allocation score system implemented in May 2005 (7). Modified lung allocation scores that include *Burkholderia* infection status together with current lung allocation score factors were then calculated for the waiting list cases. Two-sample *t* tests were used to compare demographics of continuous variables between *Burkholderia*-infected and uninfected patients. Fisher exact tests were used to compare categorical demographic information between these groups.

**Waiting list survival models.** Two multivariate Cox models were used to assess the association between *Burkholderia* infection and the mortality hazard among the 1,026 wait-listed candidates (28). In the first model, the 171 *Burkholderia*-infected wait-listed cases were categorized as infected with *B. cenocepacia*, *B. multivorans*, *B. gladioli*, or "other Bcc" (the latter category included patients infected with *Burkholderia* species other than *B. cenocepacia*, *B. multivorans*, or *B. gladioli*). The second model differed from the first only in that the *B. cenocepacia*-infected patients were further subdivided into three groups based on bacterial strain type (i.e., strain PHDC, the Midwest strain, and, as a single group, all other *B. cenocepacia* strains). Both models used time-dependent covariates for infection status and duration of *Burkholderia* infection, censored follow-up at transplant, and adjusted for lung allocation score factors affecting CF waiting list survival. These latter factors included age at waiting list entry, diabetes, six-minute-walk distance < 150 ft, New York Heart Association (NYHA) functional status, FVC (% predicted), pulmonary arterial systolic pressure, O<sub>2</sub> required at rest (L/min), body mass index, and mechanical ventilation at the time of wait-listing. In these analyses, we assumed that these factors, which previously have been shown to be associated with mortality in lung transplantation, also apply to *Burkholderia*-infected patients with CF undergoing or being considered for transplantation (7). To estimate adjusted 1- and 5-year survival probabilities for both infected and uninfected wait-listed candidates, Cox survival curves fitted to the 1,026 wait-listed candidates were estimated for a typical patient profile differing only by infection status. Time infected was taken to be zero for uninfected patients and 2 years for infected groups in reported survival estimates by infection status; approximately 63% (108/171) of patients had been infected at least this long at listing.

**Post-transplant survival models.** Two other multivariate Cox models were used to assess the hazards of infection in the 528 lung transplant recipients. In the first model, the 88 transplanted cases were categorized as infected with *B. cenocepacia*, *B. multivorans*, *B. gladioli*, or other Bcc at the time of transplant. The second model differed from the first only in that the *B. cenocepacia*-infected patients were again further subdivided into three groups: those infected with strain PHDC, those infected with the Midwest clone, or, as a group, those infected

with any other *B. cenocepacia* strains. Both models adjusted for time infected before transplant as well as the following lung allocation score factors affecting CF survival: age at time of transplant, NYHA functional status, serum creatinine, and mechanical ventilation at the time of transplantation. The 1- and 5-year adjusted post-transplant survival probabilities by infection status were obtained using the estimates from the multivariate Cox model fit to the data on the 528 transplant recipients, estimated for a typical recipient profile differing only by infection status. These survival estimates assumed zero time infected for uninfected patients and 2 years' time infected before transplant for infected patients. Significant results are reported at the  $\alpha = 0.05$  level.

**Projected benefit.** Projected transplant benefit is estimated by subtracting the area under a patient's waiting list survival curve from the area under the patient's post-transplant survival curve during a specified time interval. The result is expressed as the expected days gained from the transplant during the time interval. The projected benefit during the first year and during the first 5 years after transplantation, if a patient were to receive lung transplantation at the time of listing, was calculated for each of the 1,026 wait-listed candidates. In this calculation, Cox-based wait-list and post-transplant survival curves were estimated specific to each patient according to existing lung allocation score risk factors and *Burkholderia* infection status.

**Lung allocation scores.** Models estimating projected wait-listed candidate and transplant recipient survival according to individual risk factors also were used to calculate an updated lung allocation score (7) for each of the 1,026 wait-listed candidates that includes *Burkholderia* infection status information. The lung allocation score is based on (1) urgency, defined by the number of days a patient would be expected to live during the next year without a transplant, and (2) benefit, defined by the number of additional days a patient would be expected to live during the next year if he or she were to receive a lung transplant. Patient urgency is typically estimated using the area under a patient-specific Cox-based waiting list survival curve up to a year. Patient benefit is estimated as described above. The resulting raw lung allocation score is defined as the patient benefit measure minus the patient urgency measure. The score is then normalized to produce a range from 0 to 100 by calculating  $100 \times (\text{raw lung allocation score} + 730) / 1,095$ .

## RESULTS

### Multivariate Analysis of Wait-Listed Candidates

Few significant differences in demographic and clinical features were found between the 1,026 infected and uninfected wait-listed candidates (Table 1). *B. multivorans*-infected patients had higher functional status classifications than uninfected patients, with 55.4 versus 37.4%, respectively, in NYHA functional status 2 ( $P = 0.01$ ). A significantly greater proportion of patients infected with other Bcc (i.e., those infected with

TABLE 1. WAIT-LISTED CANDIDATES' DEMOGRAPHIC MEANS OR PROPORTIONS BY INFECTION STATUS

Variable	Uninfected (n = 855)	<i>B. cenocepacia</i> All (n = 62)	<i>B. cenocepacia</i> PHDC (n = 13)	<i>B. cenocepacia</i> Midwest (n = 17)	<i>B. cenocepacia</i> Other* (n = 32)	<i>B. multivorans</i> (n = 56)	Other Bcc <sup>†</sup> (n = 23)	<i>B. gladioli</i> (n = 30)
Age, yr	27.4	28.0	28.7	25.5	29.0	27.3	27.7	27.6
FVC, % predicted	44.7	46.0	44.9	44.7	47.1	43.6	50.1	45.1
PA systolic pressure, mm Hg	37.9	40.3	31.2	44.0	43.7	35.6	36.7	40.5
Resting O <sub>2</sub> requirement, L/min	1.6	1.6	2.2 <sup>‡</sup>	1.4	1.4	1.8	1.1	1.1
BMI	19.1	19.2	20.6	18.2	19.1	20.1	18.7	19.1
Diabetic, %	27.9	27.5	60.0 <sup>‡</sup>	13.3	23.1	35.0	36.8	28.0
Six-minute-walk < 150 ft, %	6.7	6.4	10.0	8.3	4.0	0.0	0.0	4.0
NYHA functional status, %								
2	37.4	51.6 <sup>‡</sup>	61.5	58.8	43.8	55.4 <sup>‡</sup>	47.8	33.3
3	1.4	0.0	0.0	0.0	0.0	3.6	13.0 <sup>‡</sup>	3.3
On ventilator, %	1.0	0.0	0.0	0.0	0.0	0.0	8.7 <sup>‡</sup>	0.0

Definition of abbreviations: BMI = body mass index; NYHA = New York Heart Association.

\* "B. cenocepacia Other" includes all *B. cenocepacia* strains that are not strain PHDC or Midwest clone.

<sup>†</sup> "Other Bcc" includes all *B. cepacia* complex species other than *B. cenocepacia* and *B. multivorans*.

<sup>‡</sup> Statistically significant difference from uninfected patients at  $P < 0.05$ . At this level of significance with 70 tests, 3.5 spurious differences are expected.

species other than *B. cenocepacia* or *B. multivorans*) were classified as NYHA functional status 3 when compared with uninfected patients (13.0 vs. 1.4%, respectively;  $P = 0.006$ ) and were more often ventilated (8.7 vs. 1.0%,  $P = 0.03$ ). Patients infected with *B. cenocepacia* strain PHDC required more oxygen at rest on average than uninfected patients (2.2 vs. 1.6 L/min, respectively;  $P = 0.049$ ) and were more frequently diabetic (60.0 vs. 27.9%,  $P = 0.036$ ). These differences might indicate a trend toward somewhat reduced capacity among infected patients when compared with their uninfected counterparts, although the prognosis tended to be poor for all patients with CF on the lung transplant waiting list.

Once adjusted for lung allocation score factors, the HRs and estimated 1- and 5-year adjusted survival probabilities among the 1,026 wait-listed candidates did not differ significantly by infection status (Table 2), although considerable variability was seen in observed event rates in these small groups over time (Figure 2A; see Figure E1A in the online supplement for unadjusted wait-list survival estimates by species/strain). The hazard associated with time infected before waiting list entry was not statistically significant (HR, 1.00; 95% confidence interval [CI], 0.94–1.07;  $P = 0.97$ ). The indices of concordance for model fit were approximately 70%, indicating correct ordering of mortality by the model in 70% of pairs selected from the cohort with verifiable ordering of outcomes.

#### Multivariate Analysis of Transplant Recipients

Few significant differences in demographic and clinical features were noted among the 528 lung transplant recipients (Table 3). Transplant recipients infected with *B. cenocepacia* strain PHDC or with *B. cepacia* complex species other than *B. cenocepacia* or *B. multivorans* were significantly more often classified with NYHA functional status 3 compared with uninfected recipients ( $P = 0.03$  and  $0.007$ , respectively); most uninfected recipients were classified as NYHA functional status 1 or 2. Otherwise, lung allocation score factors relating to prognosis after transplant were similar between infected and uninfected recipients.

Once adjusted for lung allocation score factors, the HRs and 1- and 5-year survival probabilities for lung transplant recipients showed several significant differences by infection status (Table 4). Lung transplant recipients infected with *B. gladioli* had significantly higher post-transplant mortality than uninfected patients (HR, 2.23; 95% CI, 1.05–4.74;  $P = 0.04$ ) and recipients infected

with *B. multivorans* (HR, 3.41; 95% CI, 1.23–9.46;  $P = 0.02$ ) (Figure 2B; see Figure E1B for unadjusted transplant survival estimates by species/strain). Survival was similar between *B. multivorans*-infected recipients and uninfected recipients (HR, 0.66; 95% CI, 0.27–1.56;  $P = 0.34$ ). Hazards for recipients infected with nonepidemic *B. cenocepacia* strains (i.e., strains other than PHDC or the Midwest clone) were also high when compared with uninfected recipients (HR, 2.52; 95% CI, 1.04–6.12;  $P = 0.04$ ) or *B. multivorans*-infected recipients (HR, 4.39; 95% CI, 1.62–11.85;  $P = 0.0035$ ). The hazard associated with time infected before transplant was not statistically significant (HR, 1.03; 95% CI, 0.94–1.13;  $P = 0.58$ ). The indices of concordance for post-transplant model fit were approximately 60%.

#### Projected Transplant Benefit and Modified Lung Allocation Scores

Projected 1- and 5-year benefits of transplantation, if transplanted at the time of initial wait-listing, and modified lung allocation scores for the 1,026 wait-listed candidates were calculated using data recorded at the time of each patient's listing and using existing lung allocation score factors, infection status, and duration of infection before listing. Projected benefit for the first year after transplantation was positive in 270 (26.3%) patients (Figure 3A); benefit was projected to be positive for 567 (55.3%) patients over the course of the first 5 years after transplantation (Figure 3B). Modified lung allocation scores for the wait-listed patients that include infection status in the assessment of patient urgency and benefit are shown in Figure 4. There was substantial variability in the lung allocation scores, and there were many infection categories that had scores overlapping with uninfected patients once all risk factors were taken into account. As expected, *B. multivorans*-infected candidates have scores similar to those of uninfected patients, as did other infection categories that did not have statistically different survival from that of uninfected patients. However, *B. gladioli* and nonepidemic strains of *B. cenocepacia* tended to have many scores below 30, which would typically put these candidates at the bottom 5% of the waiting list for lung allocation. As a measure of robustness to proportional hazards assumptions in the mortality models, we refit wait-list and post-transplant models, stratifying baseline hazard calculation by *Burkholderia* species/strain. Lung allocation scores were

TABLE 2. ADJUSTED HAZARD RATIOS, 1- AND 5-YEAR WAITING LIST SURVIVAL RATES\* BY INFECTION STATUS (n = 1,026)

Species/Strain	n (%)	HR (95% CI)	P <sup>†</sup>	1-Year Survival, % (95% CI)	5-Year Survival, % (95% CI)
Uninfected, reference group	855 (83)	1.00 (NA)	NA	80.1 (77.5–83.8)	47.3 (41.2–54.1)
<i>B. cenocepacia</i> <sup>‡</sup>	62 (6)	1.46 (0.74–2.90)	0.28	82.7 (72.3–94.5)	32.3 (15.9–65.8)
<i>B. cenocepacia</i> PHDC	13 (1)	1.06 (0.30–3.67)	0.93	78.3 (58.1–100.0)	56.2 (34.1–92.6)
<i>B. cenocepacia</i> Midwest	17 (2)	1.64 (0.65–4.12)	0.29	89.0 (76.6–100.0)	36.3 (14.7–90.0)
<i>B. cenocepacia</i> Other <sup>§</sup>	32 (3)	1.45 (0.68–3.11)	0.34	81.6 (67.9–98.1)	32.1 (13.7–74.9)
<i>B. multivorans</i>	56 (6)	1.22 (0.66–2.27)	0.52	86.5 (76.1–98.2)	28.8 (12.7–65.3)
Other Bcc <sup>  </sup>	23 (2)	1.69 (0.75–3.83)	0.21	80.1 (63.4–100.0)	0.0 (NA)
<i>B. gladioli</i>	30 (3)	1.34 (0.66–2.74)	0.42	73.5 (57.6–93.8)	39.8 (18.7–85.0)

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable.

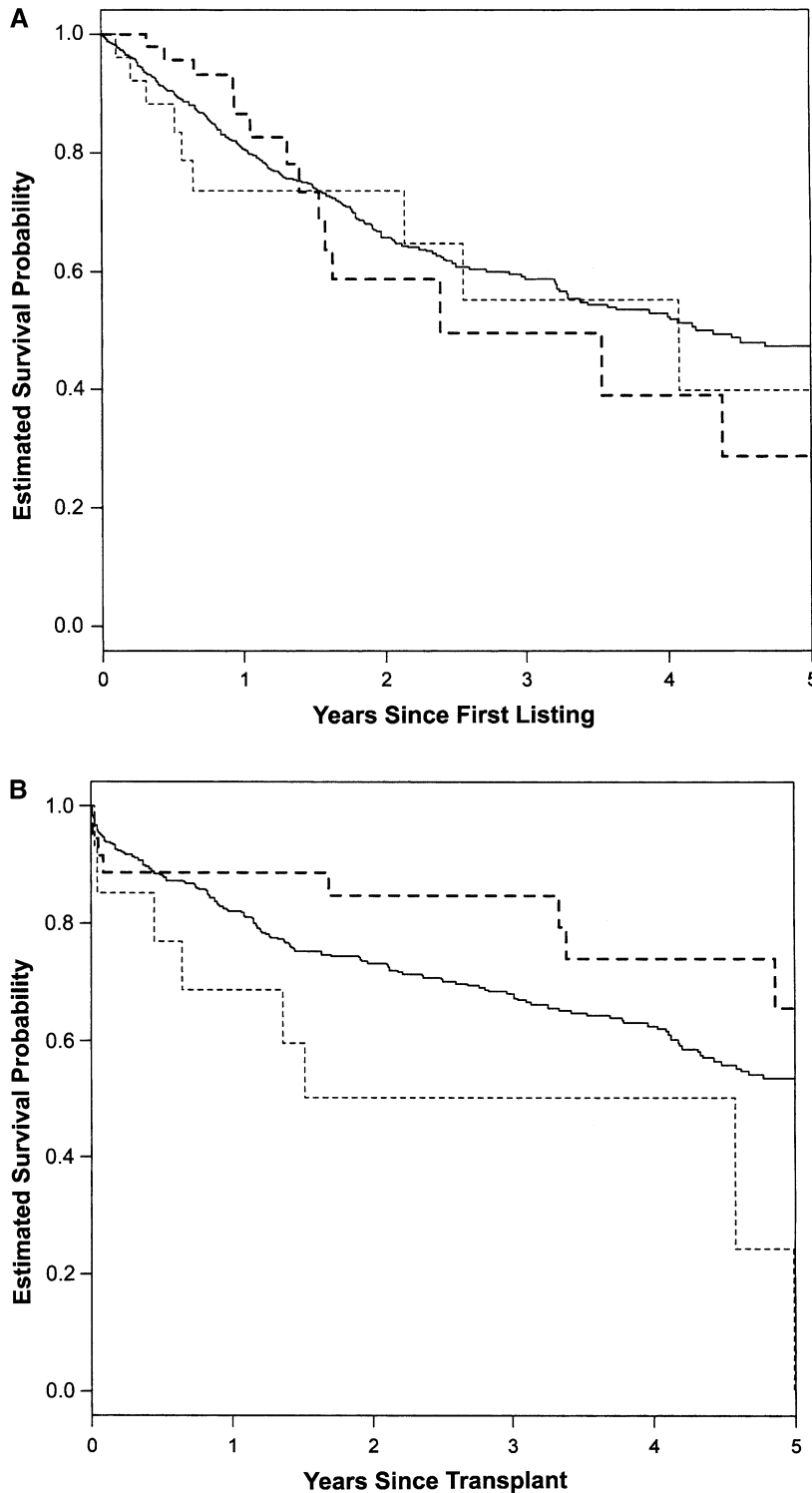
\* Survival rates reported for average covariate profile as follows: age (yr) = 27.41; probability of being diabetic = 23%; probability of having a six-minute-walk < 150 ft = 5%; probability of being classified as functional status 2 = 39%; probability of being classified as functional status 3 = 2%; FVC (% predicted) = 43.25; pulmonary arterial systolic pressure (mm Hg) = 11.93; resting O<sub>2</sub> requirement (L/min) = 1.33; body mass index = 19.02; probability of being on a ventilator = 1%; time infected (yr) = 2.0.

<sup>†</sup> P value comparing hazards between infected and uninfected (reference) group.

<sup>‡</sup> Includes results for 62 *B. cenocepacia*-infected patients produced through a separate parameterization of model.

<sup>§</sup> "*B. cenocepacia* Other" includes all *B. cenocepacia* strains that are not strain PHDC or Midwest clone.

<sup>||</sup> "Other Bcc" includes all *B. cepacia* complex species other than *B. cenocepacia* and *B. multivorans*.



**Figure 2.** Waiting list (A) and post-transplant (B) survival estimates obtained using hazards estimated with Cox models, as described in the text, adjusted for current lung allocation score factors evaluated for the average cystic fibrosis patient profile and assuming a 2-year duration of infection at transplant for infected groups. *Solid line:* uninfected patients; *bold dashed line:* *B. multivorans*; *light dashed line:* *B. gladioli*.

similar to the model assuming proportional hazards (correlation between lung allocation scores = 0.98; correlation between lung allocation score ranks = 0.93).

## DISCUSSION

Previous studies of the impact of *Burkholderia* infection on postoperative mortality in lung transplant recipients have provided conflicting results. Most studies describe poorer outcomes

among *Burkholderia*-infected recipients compared with non-infected recipients, with first-year mortality rates ranging from 15 to 80% among infected patients (19, 20, 29, 30). As a result, although current guidelines do not specifically exclude *Burkholderia*-infected patients from transplant eligibility, many centers have considered *Burkholderia* infection to be an absolute contraindication to transplantation.

However, most previous outcomes analyses assessing the impact of *Burkholderia* in lung transplantation were performed

TABLE 3. TRANSPLANT RECIPIENT DEMOGRAPHIC MEANS OR PROPORTIONS BY INFECTION STATUS

Variable	Uninfected (n = 440)	<i>B. cenocepacia</i> All (n = 31)	<i>B. cenocepacia</i> PHDC (n = 8)	<i>B. cenocepacia</i> Midwest (n = 9)	<i>B. cenocepacia</i> Other* (n = 14)	<i>B. multivorans</i> (n = 32)	Other Bcc <sup>†</sup> (n = 11)	<i>B. gladioli</i> (n = 14)
Age, yr	28.7	29.1	31.6	26.0	29.7	27.1	29.4	31.6
Years infected before transplant	NA	8.0	10.0 (Ref.)	8.1	6.8 <sup>‡</sup>	5.4 <sup>‡</sup>	4.4 <sup>‡</sup>	2.7 <sup>‡</sup>
NYHA functional status, %								
1 or 2	92.0	93.6	75.0	100.0	100.0	90.6	72.7	92.9
3	3.4	6.5	25.0 <sup>§</sup>	0.0	0.0	9.4	27.3 <sup>§</sup>	7.1
On ventilator, %	4.6	3.2	0.0	0.0	7.1	3.1	9.1	0.0
Creatinine, mg/dl	0.8	1.0	0.8	0.8	1.2	0.8	1.3	0.9

Definition of abbreviations: NYHA = New York Heart Association; Ref. = reference.

\* "*B. cenocepacia* Other" includes all *B. cenocepacia* strains that are not strain PHDC or Midwest clone.

<sup>†</sup> "Other Bcc" includes all *B. cepacia* complex species other than *B. cenocepacia* and *B. multivorans*.

<sup>‡</sup> Statistically significant difference from *B. cenocepacia* PHDC patients at  $P < 0.05$ .

<sup>§</sup> Statistically significant difference from uninfected patients at  $P < 0.05$ .

before the realization that several distinct bacterial species comprise the *B. cepacia* complex. More recently, two studies have assessed differences in outcomes relative to these species among small numbers of *Burkholderia*-infected transplant recipients. De Soyza and colleagues (31) described 11 lung transplant recipients with CF who had preoperative *B. cepacia* complex infection. Analysis of stored bacterial isolates available from nine of these patients indicated that four who died within 36 days of transplantation were infected with *B. cenocepacia*. In contrast, the remaining five patients, three of whom were infected with *B. multivorans* and two of whom were infected with *B. vietnamiensis*, were alive at the time of the report, 2.5 months to approximately 5 years after transplantation. Aris and colleagues (32) similarly described 21 lung transplant recipients who were infected preoperatively with *B. cepacia* complex; isolates from 20 patients were available for analysis. Five of 12 patients infected with *B. cenocepacia* versus none of 8 patients infected with other species (mostly *B. multivorans*) died within 5 months of transplantation (median time to death of 2.3 mo). Observations such as these, although limited by small numbers of patients, have led some centers to revise their transplantation eligibility criteria to exclude *B. cenocepacia*-infected patients while offering transplantation to patients infected with other *Burkholderia* species.

In the study presented here, we used multivariate Cox survival models to assess HRs of *Burkholderia* infection among several hundred patients with CF who were either wait-listed for lung transplantation or were lung transplant recipients. This

cohort of 1,554 patients, which includes 171 *Burkholderia*-infected lung transplant wait-listed patients, 88 *Burkholderia*-infected lung transplant recipients, and 1,295 uninfected control patients, provides the largest dataset yet analyzed to assess the relative risks of *Burkholderia* infection among transplant recipients. Because statistical power is a pervasive concern in studies of diseases affecting small patient populations, we included control cases in a 5:1 ratio. Control patients were selected to address calendar time biases; these were matched on calendar year of listing in the wait-list analyses, and year of transplant for the post-transplant analyses. The inclusion of this large set of control patients supplemented the power of our analysis to the extent possible.

We used genotypic analyses to confirm the presence of *Burkholderia* in each of the infected patients. These assays have proven superior to the routine phenotypic analyses used by most clinical microbiology laboratories, which frequently misidentify *Burkholderia* and, in general, are not capable of differentiating species within the *B. cepacia* complex (33). Confirmatory genotypic analysis of *Burkholderia* isolates from all infected patients allowed us to avoid the potential confounding due to species misidentification that may occur in retrospective studies.

We found no significant differences in survival based on *Burkholderia* infection status among persons wait-listed for lung transplantation. A possible explanation for this is that lung disease among patients entering the waiting list has already progressed to a degree that masks significant differences in

TABLE 4. HAZARD RATIO, 1- AND 5-YEAR POST-TRANSPLANT SURVIVAL RATES\* BY INFECTION STATUS ADJUSTED FOR TABLE 3 RISK FACTORS (n = 528)

Species/Strain	n (%)	HR (95% CI)	P <sup>†</sup>	1-Year Survival, % (95% CI)	5-Year Survival, % (95% CI)
Uninfected, reference group	440 (83)	1 (NA)	NA	80.3 (76.6–84.3)	53.4 (47.7–59.8)
<i>B. cenocepacia</i> <sup>‡</sup>	31 (6)	1.73 (0.73–4.11)	0.21	59.6 (40.3–88.1)	47.4 (27.6–81.2)
<i>B. cenocepacia</i> PHDC	8 (1)	1.26 (0.33–4.84)	0.74	56.4 (28.7–100.0)	56.4 (28.7–100.0)
<i>B. cenocepacia</i> Midwest	9 (2)	0.86 (0.24–3.10)	0.82	80.0 (58.1–100.0)	59.6 (33.7–100.0)
<i>B. cenocepacia</i> Other <sup>§</sup>	14 (3)	2.52 (1.04–6.12)	0.04	49.6 (27.7–88.9)	32.5 (13.2–80.2)
<i>B. multivorans</i>	32 (6)	0.66 (0.27–1.56)	0.34	88.6 (78.2–100.0)	65.6 (46.0–93.4)
Other Bcc <sup>  </sup>	11 (2)	1.39 (0.53–3.64)	0.50	66.6 (44.7–99.2)	47.2 (25.2–88.3)
<i>B. gladioli</i>	14 (3)	2.23 (1.05–4.74)	0.04	68.6 (48.0–98.1)	0.0 (NA)

For definition of abbreviations, see Table 2.

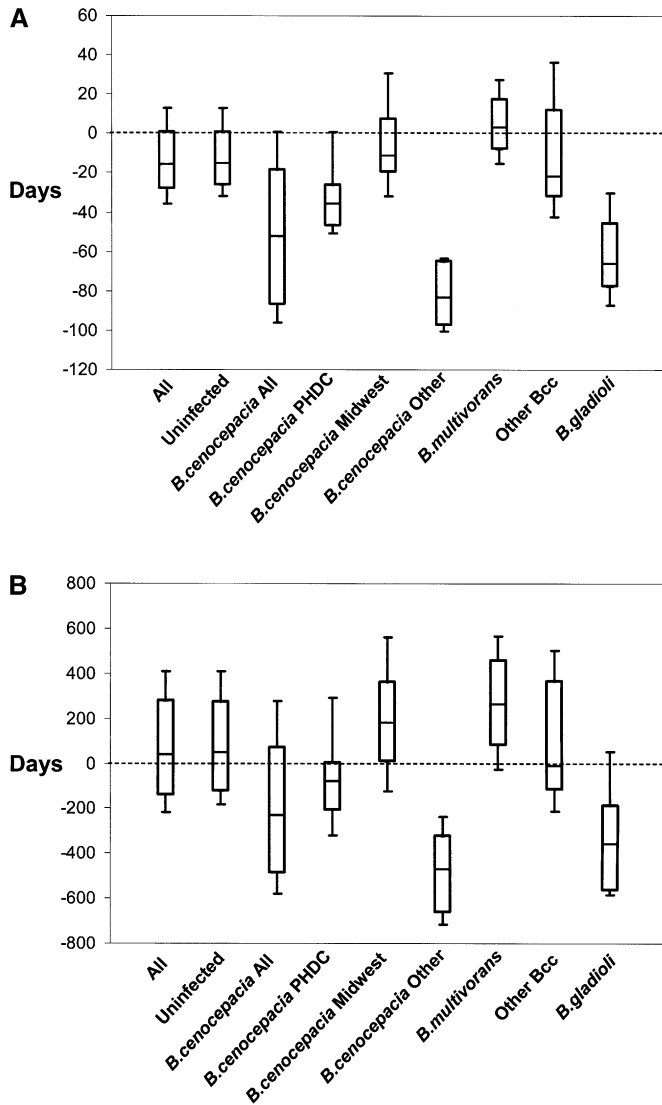
\* Survival rates reported for average covariate profile as follows: age (yr) = 28.69; probability of being classified as functional status 1 or 2 = 92%; serum creatinine (mg/dl) = 0.79; probability of being on a ventilator = 4%; time infected (yr) = 2.0.

<sup>†</sup> P value comparing hazards between infected and uninfected (reference) group.

<sup>‡</sup> Results for 31 *B. cenocepacia*-infected patients produced through a separate parameterization of the model.

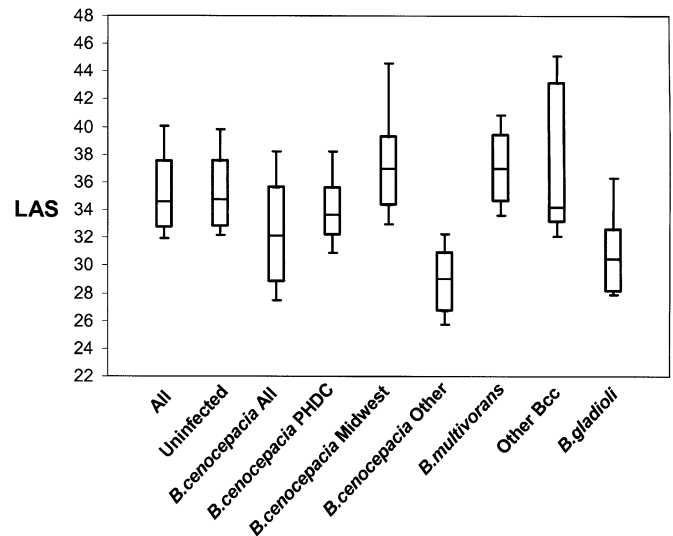
<sup>§</sup> "*B. cenocepacia* Other" includes all *B. cenocepacia* strains that are not strain PHDC or Midwest clone.

<sup>||</sup> "Other Bcc" includes all *B. cepacia* complex species other than *B. cenocepacia* and *B. multivorans*.



**Figure 3.** Projected benefit (days gained) during the first year (A) and during the first 5 years (B) after transplantation for 1,026 *Burkholderia*-infected or uninfected transplant wait-listed patients with cystic fibrosis. Benefit was calculated using current lung allocation score factors and *Burkholderia* infection status as described in the text. The horizontal lines in each box are the median adjusted benefit for the group; the boxes indicate benefit for the middle 50% of the group, and the whiskers indicate benefit for 70% of the group. Other Bcc = *B. cepacia* complex species other than *B. cenocepacia* and *B. multivorans*.

disease progression that may have been apparent earlier. It is also possible that we had insufficient power to detect real differences in these small subsets of patients. We also examined the potential of bias in this analysis due to dependent censoring for transplants occurring after implementation of the lung allocation scoring system in May 2005. Of the 1,026 patients in the wait-listed cohort, only 65 (6%) received lung transplantation after that time; the majority of these patients (57 of 65) were not *Burkholderia* infected. Our estimates of 1- and 5-year adjusted survival for uninfected wait-listed patients are very close to those reported in the pre-lung allocation score OPTN 2005 annual report for patients with CF, where 1-year adjusted survival was 84% (SE, 3%) and 5-year adjusted survival was 48% (SE, 3%) ([http://www.ustransplant.org/annual\\_reports/archives/2005/1211a\\_rec-dgn\\_lu.htm](http://www.ustransplant.org/annual_reports/archives/2005/1211a_rec-dgn_lu.htm)). This suggests minimal



**Figure 4.** Lung allocation scores (LAS) for 1,026 *Burkholderia*-infected or uninfected transplant wait-listed patients with cystic fibrosis. Scores were calculated using current LAS factors, infection status, and patients' corresponding 1-year transplant benefit and urgency as estimated from Cox multivariate models applied to our data. The horizontal lines indicate the median adjusted LAS for the group; the boxes contain the middle 50% of LAS for the group, and the whiskers cover 70% of the lung allocation scores for the group. Other Bcc = *B. cepacia* complex species other than *B. cenocepacia* and *B. multivorans*.

impact of competing risks from lung allocation score implementation on our wait-list survival analysis.

In contrast, we found that post-transplant mortality does indeed vary with *Burkholderia* species. Interestingly, in our analysis, patients infected with *B. cenocepacia*, in general, did not have a significantly increased risk of mortality. However, when this group was further subdivided into patients infected with either one of the two so-called epidemic strains common in the United States (strain PHDC and the Midwest clone) or nonepidemic strains, only the latter group had significantly increased risk compared with uninfected control subjects. The reasons for this rather unexpected result are not readily apparent and this finding must be interpreted with caution. First, more stringent patient selection for transplantation for individuals infected with *B. cenocepacia* could be playing a role. Although post-transplant risk factors between patients infected with these two epidemic *B. cenocepacia* strains and uninfected control subjects were very similar (Table 3), differential selection for transplantation not measured by these factors could be at work. Second, the definition and distinguishing microbiologic features of "epidemic strains" are not entirely clear. Strain PHDC and the Midwest clone each have been previously described as infecting numerous patients with CF in the mid-Atlantic and Midwestern regions, respectively, of the United States (34, 35). Although this epidemiology suggests an enhanced capacity for interpatient transmission and/or human infection, the microbiologic determinants of these phenotypes are unknown. It could be argued that all *Burkholderia* strains may be transmissible (or epidemic) given suitable conditions (24). Furthermore, although this epidemiology might imply that epidemic strains are more virulent in CF (compared with nonepidemic strains), the relative virulence of *Burkholderia* strains is difficult to assess in the absence of adequate models of human infection or clearly defined virulence determinants. *B. cenocepacia* strain ET12, which is common among patients

with CF in eastern Canada and the United Kingdom, has been associated with high rates of mortality in several studies involving small numbers of patients with and without lung transplantation (31, 36, 37). Thus, our findings in lung transplant recipients should not be taken to imply that all epidemic strains are less virulent than nonepidemic strains in CF. Indeed, as with strain ET12, the converse may be true. It is interesting to note that strain PHDC and the Midwest clone reside in *B. cenocepacia* *recA* subgroup B, whereas strain ET12 is a member of *recA* subgroup A. Clearly, potential differences in virulence and associated clinical outcomes between distinct *B. cenocepacia* strains require further study. This can only be accomplished by analyzing outcomes among larger cohorts of *B. cenocepacia*-infected patients whose isolates have been genotyped to ascertain strain type.

Our analysis indicates that persons infected with *B. gladioli* also have a significantly increased risk of mortality after transplantation. This species, although not a member of the *B. cepacia* complex, accounts for a significant proportion of *Burkholderia* infection in CF. Data from the BcRLR indicate that, during the last 4 years, *B. gladioli* accounted for approximately 15 to 20% of new *Burkholderia* infections among patients with CF in the United States (unpublished data). The role that *B. gladioli* plays in contributing to pulmonary disease in infected patients with CF, in general, is unknown, and only a handful of case reports describe outcomes among infected lung transplant recipients. One describes a patient who developed postoperative pulmonary, pleural space and chest wall infection with *B. gladioli* and died 6 months after transplantation (38). Another describes a patient with preoperative recurrent subcutaneous abscesses with *B. gladioli* who did not survive transplantation (39), whereas two other patients are reported to have survived despite developing postoperative wound infections (11). More recently, Kennedy and colleagues (40) described three patients with CF with chronic *B. gladioli* infection who also survived lung transplantation, although two developed post-transplant infection, one with a mediastinal abscess that required surgical debridement.

An important finding in our analyses is the lack of increased post-transplant mortality among patients with CF infected with *B. multivorans*. This species accounts for an increasing proportion of *Burkholderia* infection in CF in the United States and elsewhere (23, 41); indeed, the incidence of *B. multivorans* infection in CF in the United States is now approximately twice that of *B. cenocepacia* (unpublished data). Previous studies have suggested that, among non-transplant recipients, outcomes associated with *B. multivorans* infection are comparable to those observed with *Pseudomonas aeruginosa* infection (36). Our finding that patients infected with *B. multivorans* had post-transplant outcomes similar to uninfected patients when adjusted for other risk factors suggests that infection with this species should not be considered a contraindication to lung transplantation. It should be noted, however, that poor outcomes with *B. multivorans* infection have been reported, suggesting that, as in the case of *B. cenocepacia*, significant strain-to-strain variation in virulence is possible (42, 43).

We used the models estimating wait-listed candidate and transplant recipient survival to calculate the projected benefit of transplantation, assuming transplantation at the time of initial wait-listing, for each of the 1,026 wait-listed candidates. We found that approximately one-quarter of candidates were projected to have a benefit in the first year after transplantation. However, it is important to note that during the 10-year period included in our study, the majority of patients with CF were placed on the wait list relatively early with the expectation that an organ would not be offered, on average, for 2 years there-

after. Consequently, the projected 1-year benefit tends to be low (negative values) because at the time of listing these patients were not yet truly in need of transplantation. The projected 5-year benefit better reflects what would be expected based on the covariates known at the time of wait listing. By 5 years after transplantation, more than half of these patients were projected to have had a benefit.

We also calculated a modified lung allocation score for each wait-listed candidate that includes *Burkholderia* infection status parameter estimates in the assessment of transplant urgency and benefit. We found that lung allocation scores of *B. multivorans*-infected candidates were comparable to those of uninfected candidates, whereas those of *B. gladioli*-infected and some *B. cenocepacia*-infected candidates (those infected with nonepidemic strains) were lower. Indeed, many of these latter scores were below 30, which would place these candidates near the bottom 5% of the waiting list for lung allocation.

These findings suggest that consideration should be given to including *Burkholderia* infection status (i.e., species and possibly strain type) in the lung allocation scoring system. Although the identification of a species or strain with greater post-transplant risk would reduce the predicted post-transplant benefit of some patients, the inclusion of infection status could provide other *Burkholderia*-infected patients who currently are excluded from transplant eligibility (i.e., those infected with species not associated with increased risk) with the opportunity to receive a transplant. As with other modifications to the lung allocation scoring system, periodic reevaluation would be needed to identify changes to the lung allocation algorithm and the effects of these changes on waiting list and post-transplant survival. If a less selective population of *Burkholderia*-infected patients is transplanted than that included in our cohort, updated analyses will be needed to determine any changes in mortality that may ensue.

In summary, we have analyzed the most complete microbiologic and outcomes data available to assess lung transplantation urgency and benefit among a large cohort of *Burkholderia*-infected patients with CF. We found that patients infected with some, but not all, strains of *B. cenocepacia* are at increased risk of poor post-transplant outcome. This suggests that important differences in virulence may exist between strains within this species. Interestingly, we found that patients infected with *B. gladioli* also have a significantly increased risk of post-transplant mortality. Perhaps most importantly, we show that patients infected with *B. multivorans*, which accounts for an increasing proportion of *Burkholderia* infection in CF, have no increased risk when compared with uninfected control subjects, suggesting that they should not be excluded from lung transplantation eligibility. Of course, differences in individual host response to infection almost certainly play an important role in outcomes. Additional study is needed to better define potential interstrain differences in outcomes and to identify the bacterial and host factors involved. It is also important to note that our findings, which are based on an analysis of a biased patient population (i.e., lung transplant candidates and recipients), may not extend to clinical outcomes among *Burkholderia*-infected patients with CF as a whole. Additional study is needed to better ascertain the relative risks of infection with different *Burkholderia* species within this larger patient population. Nevertheless, our findings indicate that *Burkholderia* infection, in general, should not be considered an absolute contraindication to lung transplantation for persons with CF. Inclusion of *Burkholderia* infection status in calculating lung allocation scores is warranted.

**Conflict of Interest Statement:** None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.



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