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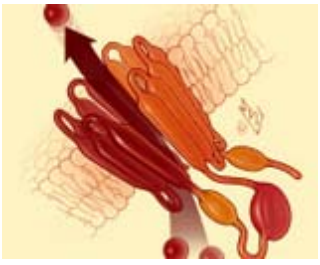



**July 2008: VOLUME 1, NUMBER 2**

## *Issues in Lung Transplantation for Cystic Fibrosis*


## In this Issue...

Over the last two decades, lung transplantation has emerged as a viable — and often the only — option for many patients with progressive life threatening obstructive lung disease and its complications. Most parents of CF patients and CF adults have some knowledge of transplantation as a treatment option, and most CF caregivers understand and/or have personal experience with the details regarding transplant referral, listing, and anticipated outcomes.

In this issue, we review 6 recently published papers relevant to transplant patient selection and outcome, with specific focus on the risk imposed by prior thoracic surgical procedures, survival and complications of transplantation in a large transplant center, stratification of risk based on resistant bacterial pathogens, and the appropriateness of lung transplantation for children with CF. Taken together, this information will enable the CF provider to better educate and counsel patients and families regarding the appropriateness of lung transplantation.

## THIS ISSUE



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***Guest Faculty Disclosures***

**Joseph M. Pilewski, MD** has disclosed no relationship with commercial supporters.

***Unlabeled/Unapproved Uses***

The author has indicated that there will be references to unlabeled/unapproved uses of drugs or products in this presentation. Alemtuzumab, inhaled cyclosporine, rapamycin, mycophenolate, tacrolimus, azathioprine, antithymocyte globulin, and cyclosporine are off-label for lung transplant.

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## LEARNING OBJECTIVES

**At the conclusion of this activity, participants should be able to:**

- Discuss with colleagues the risks and benefits of lung transplant for CF, including common complications and outcomes, and the limitations to prolonged survival for lung transplant recipients.
- Describe to colleagues the impact of various CF airway pathogens on lung transplant candidacy, and the potential impact of specific pathogens on the Lung Allocation System.
- Summarize for colleagues the controversy over lung transplant for pediatric CF patients

## COMMENTARY

Lung transplantation has evolved into a widely accepted but imperfect therapeutic option for patients with end stage lung disease, including Cystic Fibrosis (CF). Analyses from a large international patient registry reveal that survival for adult and pediatric lung transplantation has improved over time,[1,2] with survival half-life for adults increasing from 3.9 years for patients transplanted between 1988 and 1994 to 5.3 years for patients transplanted between 2000 and 2005.[1] Most of the improved survival, however, has occurred in the first year after transplant, presumably reflecting improvements in surgical techniques and reduction in early life threatening surgical and infectious complications (primary graft failure, bronchial dehiscence, and opportunistic pneumonias). The major obstacle to improved long-term outcomes for lung transplantation remains bronchiolitis obliterans syndrome (BOS), the typically progressive obstructive lung disease that afflicts almost 50% of recipients by 5 years after transplantation.[1] Unfortunately, little progress has been made towards early recognition and treatment of BOS, as studies of azithromycin[3,4] have shown only modest efficacy at best, and a multi-center trial of inhaled cyclosporine is necessary to confirm promising single center results.[5] Preliminary studies of perioperative lymphocyte depletion appear very promising;[6] however, efficacy of all the current induction strategies[7] for the prevention of BOS still need to be defined via prospective studies. Significant correlation between gastroesophageal reflux disease and bronchiolitis obliterans syndrome was demonstrated in a retrospective review, and in subsequent studies, Nissen fundoplication was shown to reverse obstructive lung disease in some patients and in the majority, slow the rate of FEV1 decline.[8] Thus, aggressive identification and management of reflux disease may improve survival in CF transplant recipients. Ultimately, a better understanding of the pathogenesis of BOS and multi-center, randomized, prospective trials of immunomodulatory agents are needed.

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As lung transplantation involves allocation of a limited number of acceptable organ donors, a recent focus of activity has been on allocating organs to patients who have the highest risk of short term mortality and the greatest likelihood of post-transplant survival – accomplished by identifying risk factors that portend a poor outcome, defined primarily as limited post-transplant survival. Progress towards improving the allocation system for lungs arrived in 2005 with institution of the Lung Allocation System (LAS) score.[9] The change in allocation from a time-based list to this disease severity allocation has alleviated the pressure for patients to be evaluated and listed (and perhaps transplanted) prematurely,[10,11] and appears to have achieved its intended goal of reducing mortality on the waiting list, at least for patients with Idiopathic Pulmonary Fibrosis. Many transplant directors have the impression that the LAS has not sufficiently shortened waiting times and reduced mortality for patients with CF, but incorporation of $pCO_2$ into the scoring system will hopefully rectify this shortcoming. Lastly, although a paper published last year by Liou et al (reviewed herein) questioned the benefit of pediatric lung transplant for CF patients, the premises of this study appear questionable and the relevance of the dataset are unclear in the new era of LAS use.[12] Most CF physicians strongly believe that lung transplant is a reasonable option for survival and quality of life in severely ill pediatric patients.

In the last year, several papers have directly or indirectly addressed issues relevant to transplant candidacy for patients with CF, and support several important conclusions. First, a 2008 study by Meachery shows that patients with prior chest surgery (including pleurodesis and lobectomy) and significant liver disease can have transplant outcomes comparable to patients with no history of pneumothorax or chest surgery. These data (reviewed herein) suggest that prior pneumothorax, much like CF liver disease and need for mechanical ventilation,[13] are no longer appropriate contraindications for lung transplantation. Second, a number of conclusions are emerging regarding the impact of resistant bacterial infections on transplant outcomes for CF, including: 1) patients with pan-resistant *Pseudomonas aeruginosa* infections do not have significantly worse outcomes (Meachery et al), and patients with sensitive strains of *P. aeruginosa* may have improved outcomes compared to other recipients (Hadjiliadis et al, reviewed in this issue); and 2) patients infected with *Burkholderia cenocepacia* or *B. gladioli* appear to have significantly shorter survival than patients without these organisms with other *Burkholderia* species (Alexander, Boussaud, Murray, all reviewed herein); however, patients with *B. multivorans* and perhaps those with specific strains of *B. cenocepacia* appear to have outcomes similar to patients infected with other typical CF pathogens. Thus, not all *B. cepacia* species are created equally, and further investigation is needed before patients with Burkholderia species are categorically denied an opportunity for lung transplantation.

**References**


1. Trulock EP, Christie JD, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: 24th Official Adult Lung and Heart-Lung Transplantation Report – 2007. *J Heart Lung Transplant.* 26: 782-795, 2007.
2. Aurora P, Boucek MM, Christie J, Dobbels F, et al. Registry of the International Society for Heart and Lung Transplantation: tenth official pediatric lung and heart/lung transplantation report--2007. *J Heart Lung Transplant.* 26:1223-1228, 2007.
3. Gottlieb J, Szangolies J, Koehnlein T, Golpon H, Simon A, Welte T. Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. *Transplantation.* 85:36-41, 2008.
4. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med.* 172:772-775, 2005.
5. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med.* 354:141-150, 2006.
6. McCurry KR, Iacono A, Zeevi A, et al. Early outcomes in human lung transplantation with Thymoglobulin or Campath-1H for recipient pretreatment followed by posttransplant tacrolimus near-monotherapy. *J Thorac Cardiovasc Surg.* 130 528-537, 2005.
7. Hachem RR, Edwards LB, Yusen RD, Chakinala MM, Alexander Patterson G, Trulock EP. The impact of induction on survival after lung transplantation: an analysis of the International Society for Heart and Lung Transplantation Registry. *Clin Transplant.* 2008 Apr 24. [Epub ahead of print]
8. Cantu E 3rd, Appel JZ 3rd, Hartwig MG, et al. J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. *Ann Thorac Surg.* 78:1142-51; discussion 1142-1151, 2004.
9. Davis SQ, Garrity ER Jr. Organ allocation in lung transplant. *Chest.* 132:1646-1651, 2007.

10. Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. *Am J Respir Crit Care Med.* 171:1053-1059, 2005.
11. Liou TG, Adler FR, Cahill BC, et al. Survival effect of lung transplantation among patients with cystic fibrosis. *JAMA.* 286:2683-2689, 2001.
12. Sweet SC, Aurora P, Benden C, et al; International Pediatric Lung Transplant Collaborative. Lung transplantation and survival in children with cystic fibrosis: solid statistics--flawed interpretation. *Pediatr Transplant.* 12:129-136, 2008.
13. Bartz RR, Love RB, Leverson GE, Will LR, Welter DL, Meyer KC. Pre-transplant mechanical ventilation and outcome in patients with cystic fibrosis. *J Heart Lung Transplant.* 22:433-438, 2003.



# OUTCOMES OF LUNG TRANSPLANTATION FOR CYSTIC FIBROSIS

Meachery G, De Soyza A, Nicholson A, et al. **Outcomes of Lung Transplantation for Cystic Fibrosis in a large United Kingdom cohort.** *Thorax.* 2008.

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An important consideration in discussing lung transplantation with CF patients is outcomes. A number of single center reports of outcomes for patients with CF have been published over the last few decades, and the annual report of the Registry of the International Society for Heart Lung Transplantation summarizes multi-center outcome data and risk factors for 1 and 5 year survival.[1] In the most recent large single center report, Meachery et al report on outcomes of adult and pediatric patients who underwent lung or heart-lung transplantation at Freeman Hospital (Newcastle-upon-Tyne, England) from 1989 to 2007.

Of the 176 patients who underwent transplantation, the majority (167) were adults and most (168) underwent bilateral sequential lung transplantation from cadaveric donors; the median age at transplantation was 26.2 years. All bilateral transplants were done with cardiopulmonary bypass, and all patients underwent a 3 day induction protocol with anti-thymocyte globulin and intravenous methylprednisolone (2 mg/kg), followed by triple immunosuppressive therapy with cyclosporine, prednisolone, and azathrioprine. Notable pre-morbid conditions included significant pleural disease (12% had prior therapy for pleurodesis, including 6 patients with medical or surgical pleurodesis); outcomes were no worse in these patients compared to the larger cohort. Similarly, 12% of the patients used non-invasive ventilation, and outcomes in this subgroup were not appreciably different from larger cohort. Significant malnutrition was common in the population reviewed, with median BMI of 18.6 and some BMI as low as 12. Survival for the 176 patients was 84% at one year, 70% at 3 years, 62% at five years, and 51% at ten years. The most frequent (51%) cause of death was bronchiolitis obliterans syndrome (BOS), a chronic obliteration of the small airways that eventuates in severe obstructive lung disease; deaths due to infections accounted for 26% of all recipient deaths. Pulmonary function among survivors was excellent (78% predicted FEV1 at 1 year), despite frequent acute cellular rejection (41% at one month). Post-transplant survival for patients with multiply or pan-resistant *Pseudomonas aeruginosa* infections pre-transplant were not appreciably different from those with sensitive *P. aeruginosa* or other infections.

In this large single center review of lung transplant outcomes for CF, several important practices are supported by retrospective data. First, patients with prior pneumothoraces, including pleurodesis procedures, can, in the care of an experienced transplant team, have comparable outcomes. Second, using an induction protocol of lymphocyte depletion followed by three-drug immunusuppression, outcomes in this experienced center for a cohort transplanted from 1989 to the present yielded comparable long-term survival relative to the aggregate data reported in the international registry for patients transplanted from 1994 to 2005.[1] Third, the major limitation to long-term survival for CF patients is bronchiolitis obliterans syndrome (BOS). Until the pathophysiology of bronchiolitis obliterans is understood and new preventive or treatment approaches are identified, outcomes from lung transplantation are likely to be inferior to those of other solid organs.

Fourth, patients with multiply or pan-resistant *P. aeruginosa* and other infections — but excluding *Burkholderia cepacia* — did not fare worse than those with sensitive organisms. This finding supports prior research and indicates that pan-resistant *P. aeruginosa* infection should not be perceived as a contra-indication to lung transplant for patients with CF.

**References**


1. Trulock EP, Christie JD, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: 24th Official Adult Lung and Heart-Lung Transplantation Report – 2007. *J Heart Lung Transplant.* 2007;26(8):782-795.




# OUTCOME AFTER LUNG TRANSPLANTATION IN CF PATIENTS INFECTED WITH PAN-RESISTANT BACTERIA OTHER THAN *BURKHOLDERIA CEPACIA*

Hadjiliadis D, Steele MP, Chaparro C, et al. **Survival of lung transplant patients with cystic fibrosis harboring pan-resistant bacteria other than compared with patients harboring sensitive bacteria.** *J Heart Lung Transplantation.* 2007;26(8):834-838.

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Beginning with papers by Aris et al in 1997[1] and others,[2] there has been some controversy over the impact of pan-resistant bacteria other than *Burkholderia cepacia* on outcome from lung transplantation for CF. In this report, Hadjiliadis and colleagues retrospectively review the experience at two large lung transplant centers (University of Toronto and Duke University). The Toronto cohort consisted of 53 patients transplanted between 1988 and 2001, while the Duke cohort comprised 46 patients transplanted between 1992 and 2001. Immunosuppression was similar at the two centers, with a maintenance regimen of cyclosporine (or tacrolimus), azathioprine, and corticosteroids. Some patients in both centers were treated with rabbit anti-thymocyte globulin (RATG), and some received mycophenolate mofetil in lieu of azathioprine. Patients routinely received intravenous antibiotics for two weeks and inhaled tobramycin for three months post-transplant.

Pan-resistant *Pseudomonas aeruginosa* was defined as those isolates having resistant or intermediate susceptibility to one antibiotic from each class effective against these bacteria (anti-pseudomonal penicillins, cephalosporins, carbapenems, quinolones, and aminoglycosides). Patients in the group with pan-resistant *P. aeruginosa* (n=45) had worse outcomes by overall comparison of survival to those with sensitive organisms (n=58). The difference in survival was appreciable up until two years after transplant, after which the survival curves were comparable. In addition, patients in the pan-resistant *P. aeruginosa* group tended to have infection as a more common cause of death than the sensitive group; however, pan-resistant *P. aeruginosa* was directly responsible for death in only 3 of the 45 patients in this group.

This is one of the larger series comparing outcomes in CF patients infected with pan-resistant *P. aeruginosa*, and provides several interesting findings. Patients in the pan-resistant group comprised almost half the study population, highlighting the commonality of highly resistant *P. aeruginosa* in the CF population with end stage lung disease. While the authors' conclusion that patients with pan-resistant *P. aeruginosa* have a statistically worse outcome than those with sensitive *P. aeruginosa* appears substantiated, outcomes in the pan-resistant group were comparable to those in the UNOS registry. Thus, a corollary point to emphasize is that patients with sensitive *P. aeruginosa* appear to have a better outcome than other CF patients undergoing transplantation. A mechanism for this epidemiological observation is unclear; however, one possibility is that the sputum cultures reflect both sinus and lung microbiology. In turn, those in the sensitive group may have more common eradication of *P. aeruginosa* in the remaining trachea and sinuses, leading to lesser levels of airway stimulation by residual bacteria or bacterial products (like lipopolysaccharide) that may stimulate an immune response in the lung allograft[3], leading to allograft dysfunction and worse outcome. Against this notion is that the incidence of bronchiolitis obliterans syndrome appeared similar in the 2 groups. Nevertheless, as the

authors propose, both groups had very good outcomes, leading to the conclusion that patients with more resistant *P. aeruginosa* species should not be excluded from consideration for transplantation. Rather, the results of this study can be used to more carefully inform potential transplant candidates of their risks and outcomes, and also elevate the level of surveillance for early complications in this common group of CF lung transplant recipients.

**References**


1. Aris RM, Gilligan PH, Neuringer IP, et al. The effects of pan-resistant bacteria in cystic fibrosis patients on lung transplant outcome. *Am J Respir Crit Care Med.* 1997;155(5):1699-1704.
2. Dobbin C, Maley M, Harkness J, et al. The impact of pan-resistant bacterial pathogens on survival after lung transplantation in cystic fibrosis: results from a single large referral centre. *J Hosp Infect.* 2004;56(4):277-282.
3. Garantziotis S, Palmer SM, Snyder LD, et al. Alloimmune lung injury induced by local innate immune activation through inhaled lipopolysaccharide. *Transplantation.* 2007;84(8):1012-1019.


## IMPACT OF BURKHOLDERIA INFECTION ON LUNG TRANSPLANTATION IN CYSTIC FIBROSIS

Murray S, Charbeneau J, Marshall BC, Lipuma JJ. **Impact of Burkholderia Infection on Lung Transplantation in Cystic Fibrosis.** *Am J Respir Crit Care Med.* 2008 Jun 5 [Epub ahead of print].

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There remains considerable debate regarding whether CF patients infected with *Burkholderia* species are appropriate candidates for lung transplantation. Studies in the 1990s indicated that patients infected with *B. cepacia* had a high risk of post-transplant mortality,[1] and over time, fewer and fewer transplant centers have offered transplant evaluation and listing for patients with this infection. Over the last decade or more, Lipuma (one of the authors of this report) and colleagues have contributed immensely to understanding the microbiology of *Burkholderia* species, first by distinguishing this group of pathogens from *Pseudomonas*, then more recently identifying genotypically distinct species that appear to impact differently on transplant outcomes. Two recent reviews focus on *Burkholderia cepacia* complex (discussed below), while this paper by Murray et al examines the impact of the common *Burkholderia* species on transplant outcome.

The authors performed a multivariate Cox survival analysis of transplant outcomes for CF patients infected with *Burkholderia* species, using two large databases (the CF Foundation patient registry, and the Scientific Registry of Transplant Recipients [SRTR]) to identify cohorts of over 1000 transplant candidates and over 500 recipients. Using the data available from the *Burkholderia* Research Laboratory and Repository, the authors were able to assess the hazards of different *Burkholderia* species, and model changes in the UNOS Lung Allocation Score to incorporate the impact of *Burkholderia* infection on transplant outcome.

The authors identified 5 controls (not infected with *Burkholderia* species) for each wait-listed patient infected with a *Burkholderia* species, yielding a data set of 171 wait-listed *Burkholderia* infected patients and 855 controls. Multivariate analysis of these cohorts, using factors known to impact outcome in CF patients, and factored into the Lung Allocation System score, revealed that while there were no appreciable statistical differences, there was wide variability in hazard ratios and 1 and 5 year survival among *Burkholderia*-infected and uninfected transplant candidates. In contrast, *Burkholderia* infection significantly impacted on post-transplant survival:

- Patients infected with *B. gladioli* (n=14) had a significantly higher post-transplant mortality than uninfected recipients and recipients infected with *B. multivorans* (a conclusion similar to the recent paper by Kennedy et al.[2])
- Recipients infected with *B. multivorans* (n=32) prior to transplant had no appreciable difference in mortality compared to uninfected patients.

- Overall, transplant recipients infected with *B. cenocepacia* (n= 31) prior to transplant did not have an overall worse 1 and 5 year survival compared to uninfected patients.
- In contrast, subgroup analysis revealed that patients infected with non-epidemic *B. cenocepacia* strains (ie, strains other than the 2 epidemic strains in this dataset – the Midwest clone and PHDC) prior to transplant had a significantly higher risk of mortality compared to uninfected recipients or recipients infected with *B. multivorans*.
- Incorporation of the outcome data from this dataset into the LAS score would reduce the score for transplant candidates infected with *B. gladioli* and non-epidemic strains of *B. cenocepacia*, but have no significant impact for patients infected with other *Burkholderia* strains.

This report has several important conclusions that are relevant to potential CF transplant patients, to transplant centers that evaluate CF patients, and to the organ allocation system in the US. First, the data strongly support previous reports from other smaller series that transplant candidates infected with *Burkholderia* species other than *B. cenocepacia* and *B. gladioli* do not have excessive mortality compared to CF candidates not infected with *Burkholderia* species. Second, among patients infected with *B. cenocepacia*, there appear to be strain differences such that the excess mortality is attributable entirely to non-epidemic strains (in this series, strains other than the Midwest and PDHF clones). This result was surprising to the authors and is currently not easily explained. Clearly, there may be discordance between transmissibility and virulence, though previous reports regarding the ET12 strains of *B. cenocepacia* prevalent in Canada and the United Kingdom suggest that this epidemic strain is more virulent in CF, irrespective of transplant status. Third, the authors propose an interesting and logical modification to the Lung Allocation System that would incorporate the impact of *Burkholderia* infection on survival into the individual score. The size of this dataset and the robustness of the statistical analysis suggest that this is reasonable; however, ideally the proposed changes would be validated against a separate dataset, and the impact of the $pCO_2$ on outcome and LAS would be analyzed prior to being incorporated. Lastly, this report indicates that the excess mortality associated with *B. gladioli* and non-epidemic strains of *B. cenocepacia* occurs in the first 6 months after transplant, and while the cause of death is not reported in this important manuscript, these data suggest that more aggressive or alternative antibiotic regimens targeted at preventing early infection may improve outcome and make transplant a reasonable option for all CF patients.

**References**


1. Aris RM, Gilligan PH, Neuringer IP, et al. The effects of pan-resistant bacteria in cystic fibrosis patients on lung transplant outcome. *Am J Respir Crit Care Med.* 1997;155(5):1699-1704.
2. Kennedy MP, Coakley RD, Donaldson SH, et al. *Burkholderia gladioli*: five year experience in a cystic fibrosis and lung transplantation center.*J Cyst Fibros.* 2007;6(4):267-273.

# OUTCOME AFTER LUNG TRANSPLANTATION IN CF PATIENTS INFECTED WITH *BURKHOLDERIA CEPACIA* COMPLEX

Alexander BD, Petzold EW, Reller LB, et al. **Survival after lung transplantation of cystic fibrosis patients infected with *Burkholderia cepacia* complex.** *Am J Transplant.* 2008; 8(5):1025-1030.

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Boussaud V, Guillemain R, Grenet D, et al. **Clinical Outcome Following Lung Transplantation in Cystic Fibrosis Patients Colonized With *Burkholderia Cepacia* Complex: Results From Two French Centers.** *Thorax.* 2008 Apr 11. [Epub ahead of print]

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Alexander et al. and Boussaud et al. report comparative analyses of transplant outcomes for CF patients infected with *Burkholderia cepacia* complex (*Bcc*). The Alexander study compares outcomes for 16 patients infected with Bcc (7 with *B. cenocepacia*) and transplanted at Duke University between 1992 and 2002 to 59 patients not infected with *Bcc*. The Boussaud study reports on 22 CF patients infected with *Bcc* (8 with *B. cenocepacia*) and transplanted between 1990 and 2006 at 2 centers in France. All patients received triple immunosuppression therapy with a calcineurin inhibitor, azathioprine or mycophenolate, and corticosteroids; some patients in the French study received induction lymphocyte depletion with anti-thymocyte globulin, while patients in the Duke study received an interleukin-2 receptor agent perioperatively. All received post-operative systemic antibiotics for at least 2 weeks after transplantation, and inhaled antibiotics were continued for variable time periods after transplantation.

In the Alexander study, survival rates for patients infected with *B. cenocepacia* were significantly lower than for patients infected with other species, and patients with *B. cenocepacia* were 6 times more likely to die in the first year after transplantation (1 year survival 89-92% for non-*Burkholderia* and *Bcc* species other than *B. cenocepacia* versus 29% for *B. cenocepacia* infected patients). Similarly, in the Boussaud study, patients infected with *B. cenocepacia* prior to transplant (n=8) had higher mortality rates than patients infected with other *Burkholderia* species (n=14), while patients infected with strains other than *B. cenocepacia* did not have a statistically higher mortality risk compared to patients not infected with Bcc species. Three of the 6 deaths in *B. cenocepacia* patients occurred in the post-operative period and were directly attributable to *B. cenocepacia* infection, and 5 year survival in the *B. cenocepacia* patients was 0% compared to ~60% in the non-*B. cenocepacia* cohort.

These studies contribute to an emerging consensus that for CF patients, infection with *B. cenocepacia* (Genomovar III) is a strong risk factor for increased post-operative morbidity and mortality. The sub-species of *B. cenocepacia* was not defined in the Alexander study. In the Boussaud study, 7 of the 8 *B. cenocepacia* strains were *recA* A and not the epidemic strain ET12, suggesting that the patients in their study would be categorized in the Murray study with the group non-epidemic strains of *B. cenocepacia*. These data raise the intriguing possibility that the *recA* A strains of *B. cenocepacia* are responsible for the increased mortality observed in the numerous studies published over the last few years. Clearly, further correlation of molecularly characterized species with outcomes is needed to fully resolve this question and determine definitively whether it is ethically appropriate to exclude all patients with *B. cenocepacia* from lung transplantation. As of now, the French centers are not excluding *B. cenocepacia*, and at least some centers in the US (Pittsburgh) and Canada (Toronto) are evaluating patients with *B. cenocepacia*.

Lastly, the Boussaud study highlights the high rate of airway colonization and infection with all *Burkholderia* species after transplantation, as 15 of the 20 patients with evaluable cultures had *Burkholderia* species identified in post-operative cultures (5 of 6 *cenocepacia*, 9 of 11 *multivorans*, and 3 of 3 *vietnamiensis* or *stabilis*). This raises the possibility that outcomes could be improved in these patients with more effective antibiotics, perhaps by inhalation, particularly given the limited activity of colistin and tobramycin against *Burkholderia* species.

## PEDIATRIC LUNG TRANSPLANTATION: BENEFIT OR HARM?

Liou TG, Adler FR, Cox DR, Cahill BC. **Lung Transplantation and Survival in Children with Cystic Fibrosis.** *N Engl J Med.* 2007;357(21): 2143-2152.

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Previous studies have suggested that lung transplantation for CF confers both survival and quality of life benefits in appropriately selected patients. As pediatric lung transplantation is much less common compared to adult lung transplantation, some have questioned whether the prior studies had adequate power to be valid. Liou and colleagues therefore performed a proportional hazards analysis on a cohort of CF patients identified using the CF Foundation patient registry and data from the Organ Procurement and Transplant Network to identify variables that were associated with change in survival. They then used 3 identified covariates to estimate the effect of transplantation on patient survival.

In addition to transplantation, 4 variables were identified that impacted on survival — *Burkholderia cepacia* infection, diabetes, infection with *Staphylococcus aureus*, and age. *B. cepacia* infection was associated with shortened survival with or without transplantation, whereas diabetes was associated with shorter pre-transplant survival, and age and *S. aureus* infection were associated with shorter post-transplant survival. Using these variables as covariates, the authors estimated the benefit or harm of transplant: of the 514 children on the waiting list during the analysis period of 1992-2002, they estimated clear survival advantage for only 5 patients, risk of harm for 315 patients, and neither benefit nor harm for 194 patients. The authors conclude that benefit from lung transplantation cannot be assumed for children with CF, and suggest that a randomized trial is warranted to resolve this uncertainty definitively.

This study has created significant consternation among CF caregivers, transplant physicians, and parents of patients with CF. The provocative conclusion based on a state of the art statistical analysis that appears sound has led to a rapid re-analysis of the data and detailed critiques.[1,2] The cruxes of the argument against the Liou et al paper's conclusions are:

- the covariates used for the survival model were obtained 2 or more years prior to transplant, thereby introducing bias against transplantation;
- many covariates thought to predict short-term mortality, such as $pCO_2$, need for mechanical ventilation, use of supplemental oxygen, and change in pulmonary function over time, were not included in the model, potentially biasing against transplant benefit;
- the identified covariates may have changed between listing and transplant; however values from listing were used to calculate hazard ratios. This may have over-estimated survival on the transplant list and biased against transplant as a beneficial procedure;
- the analysis was limited to survival as the only outcome measure and was not able to evaluate for quality of life benefit.

Perhaps most importantly, the data set was derived when decisions regarding transplant listing and procedure were not based on severity of illness. The LAS score was instituted in 2005, applies to patients 12 and older, and attempts to direct organs to patients with the highest risk of death and greatest benefit after transplantation. Thus, only an analysis of outcomes with the LAS will determine the relative benefit of lung transplantation for children, and the proposal for a randomized trial has been resoundingly opposed by most in the CF and transplant communities.

### References


1. Sweet SC, Aurora P, Benden C, et al. International Pediatric Lung Transplant Collaborative. Lung transplantation and survival in children with cystic fibrosis: solid statistics--flawed interpretation. *Pediatr Transplant.* 2008;12(2):129-136.
2. Aurora P, Spencer H, Moreno-Galdó A. Lung transplantation in children with cystic fibrosis: a view from Europe. *Am J Respir Crit Care Med.* 2008;177(9):935-936.


## CME/CNE INFORMATION

### Accreditation Statement — back to top

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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### Credit Designations — back to top

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PHYSICIAN POST-TEST

NURSE POST-TEST

DIETICIAN POST-TEST

PHYSICAL THERAPIST POST-TEST

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## Post-Test — back to top

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## Statement of Responsibility — back to top

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME/CE activity.

## Intended Audience — back to top

This activity has been developed for Pulmonologists, Pediatric Pulmonologists, Gastroenterologists, Pediatricians, Infectious disease specialists, Respiratory therapists, Dieticians, Nutritionists, Pharmacists, Nurses, and Physical therapists.

## Learning Objectives — back to top

At the conclusion of this activity, participants should be able to:

- Discuss with colleagues the risks and benefits of lung transplant for CF, including common complications and outcomes, and the limitations to prolonged survival for lung transplant recipients.
- Describe to colleagues the impact of various CF airway pathogens on lung transplant candidacy, and the potential impact of specific pathogens on the Lung Allocation System.
- Summarize for colleagues the controversy over lung transplant for pediatric CF patients

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