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Correlation Between Sinus and Lung Cultures in Lung Transplant Patients with Cystic Fibrosis

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Abstract

Introduction—Lung transplantation has revolutionized the treatment of end-stage pulmonary disease due to cystic fibrosis. However, infection of the transplanted lungs can lead to serious complications including graft failure and death. While many of these patients have concurrent sinusitis, it is unclear if bacteria from the sinuses can infect the allograft.

Methods—This is a single-institution retrospective study of all patients who underwent lung transplantation for cystic fibrosis from 2005 to 2015 at Duke University Hospital. Pre- and post-transplant nasal and pulmonary cultures obtained via nasal endoscopy and bronchoalveolar lavage (BAL), respectively, were analyzed.

Results—A total of 141 patients underwent 144 lung transplants. Sinus cultures were available for 76 patients (12 pre-transplant, 42 post-transplant, 22 both pre- and post-transplant). Pre-transplant BAL cultures were available for 139 patients, and post-transplant BAL cultures were available for all patients. *Pseudomonas aeruginosa* (PsA) and Methicillin-Resistant *Staphylococcus aureus* (MRSA) were the most common organisms cultured. There was a significant correlation between pre-transplant sinus and post-transplant BAL cultures for PsA ($p = 0.003$), MRSA ($p = 0.013$) and *Burkholderia cepacia* ($p = 0.001$).

Conclusions—There was a high correlation between pre-transplant sinus cultures and post-transplant BAL cultures for PsA, MRSA and *Burkholderia* sp. This suggests that the paranasal sinuses may act as a reservoir for allograft colonization in patients with cystic fibrosis. Further studies are needed to determine if treatment of sinusitis affects allograft colonization and transplant outcomes.

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Keywords

sinusitis; cystic fibrosis; lung transplant; sinus culture

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease due to a genetic defect in the cystic fibrosis transmembrane conductance regular (CFTR) protein. The inherited mutation results in a dysfunctional CFTR protein with a chloride-ion exchange disorder that produces nasal and pulmonary secretions of high viscosity due to altered electrolyte composition. It is the most commonly inherited, lethal disease amongst Caucasians, affecting approximately 30,000 people in the United States.¹ Sinonasal manifestation of disease include chronic rhinosinusitis (CRS), while pulmonary manifestation includes recurrent pulmonary infections and bronchiectasis resulting in progressive decline of pulmonary function with end stage respiratory failure.

In the last twenty years, lung transplantation has emerged as an effective treatment option for CF patients with end-stage pulmonary disease.² However, bacterial colonization and infection of the allograft with organisms such as *Pseudomonas aeruginosa* (PsA), *Achromobacteria xylosoxidans*, *Burkholderia cepacia*, methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA, MRSA) are common and are associated with poor transplant outcomes.^{3–5} Inhaled and systemic antibiotics therefore play important roles in the post-transplant period. However, it is also important to identify and address the sources of allograft infection.

Although several studies in the general CF population have shown a correlation between bacterial strains cultured in the sinuses and lungs,^{6–8} only a few studies have reported this correlation in patients with CF who have undergone lung transplantation.^{9–11} By analyzing the pre-transplant sinus cultures in relation to post-transplant BAL cultures, the main objective of this study is to assess whether pre-existing bacteria in the paranasal sinuses can seed the lung allograft, which is presumed to be uncolonized at the time of transplant surgery.

Materials & Methods

This study was approved by the Institutional Review Board at Duke University Medical Center. The United Network for Organ Sharing (UNOS) database was used in conjunction with the Duke Enterprise Data Unified Content Explorer (DEDUCE) to identify all patients with cystic fibrosis who underwent lung transplantation from July 1, 2005 to June 30, 2015 at Duke University Hospital. The electronic medical records of subjects were reviewed to extract data regarding clinical history, as well as sinus and BAL cultures. Culture data pertaining to bacteria, fungus, and mycobacteria were collected. For bacteria, the presence of five specific organisms associated with CF was noted: PsA, MRSA, *Stenotrophomonas* sp., *Burkholderia* sp., and *Achromobacter* sp.

Pre- and post-transplant sinus culture results, as well as pre-and post-transplant BAL culture results were reviewed. All sinus cultures were obtained via nasal endoscopy in the office or in the operating room by an otolaryngologist. Pre-transplant BAL cultures were routinely obtained at the time of transplant from the recipient lungs, and serial post-transplant BAL cultures were routinely obtained one week after transplant, and then every one to three months for at least one year. Cumulative culture results were noted for each patient in the pre- and post-transplant periods separately. Chi-square test using SPSS (Armonk, NY) was performed to determine if there was a significant correlation between the bacteria identified on pre-transplant sinus and post-transplant BAL cultures. A p -value < 0.05 was considered significant.

Results

A total of 144 lung transplantations for cystic fibrosis was performed during the study period. The mean age at transplantation was 28.7 years (range: 13 – 62 year), with 63.9% (92/144) being female. The mean duration of follow up after transplant was 50 months. All patients underwent bilateral lung transplant, with the exception of one patient who underwent single lung transplant due to prior history of aspergillus infection requiring pneumonectomy (Table I).

Sinus culture results were available for 76 patients. Of these, 34 patients had pre-transplant sinus cultures, obtained at a mean of 7 months before transplant. 64 patients had post-transplant sinus cultures, obtained at a mean of 14 months after transplant. Pre-transplant BAL cultures were available for 139 of the 144 patients, while all patients had post-transplant BAL culture results available. Frequencies and percentages for each organism are noted in Tables II and III. PsA and MRSA were the predominant organisms in both sinus and BAL cultures before and after lung transplant. The percentage of patients with MRSA and PsA sinus colonization after lung transplant was greater than pre-transplant.

When comparing pre-transplant sinus cultures and post-transplant BAL cultures, there was a significant correlation for *Pseudomonas* ($p = 0.003$), MRSA ($p = 0.013$), and *Burkholderia* ($p = 0.001$). In contrast, there was no significant correlation for *Achromobacter* ($p = 0.696$), *Stenotrophomas* ($p = 0.548$), and fungus ($p = 0.650$) (Table IV). When comparing post-transplant sinus cultures with post-transplant BAL cultures, significant correlation was also observed for *Pseudomonas* ($p = 0.031$), MRSA ($p = 0.014$), and *Burkholderia* ($p = 0.001$) (Table V).

A sub-group analysis of the twenty-seven patients with correlating pre-transplant sinus and post-transplant BAL cultures for PsA, MRSA, and *Burkholderia* was performed (Table VI). 12 of the 27 patients (44.4%) had positive post-transplant BAL cultures within one week of lung transplant, despite the routine use of prophylactic systemic antibiotics at the time of transplant. One-week conversion rates were similar for the three bacteria: PsA (9/19, 47.4%), MRSA (4/7, 57.1%) and *Burkholderia* (1/3, 33.3%). 13 of the 15 remaining patients eventually had positive correlating BAL cultures within one year after transplant. After conversion, subsequent BAL cultures were typically positive as well despite recent antibiotic use.

Discussion

The recalcitrant and severe CRS that characterizes cystic fibrosis is associated with the development of multi-drug resistant bacterial infections. This potentially results in recurrent pulmonary infections with decline in pulmonary function and end stage respiratory failure, precipitating the need for lung transplantation. Advances in lung transplantation have provided CF patients with a new avenue to improve quality-of-life and survival, with their livelihood intricately tied to the health and longevity of the allograft. However, these patients frequently develop recurrent pulmonary infections of their allografts following transplant.

Prior studies have shown a correlation between bacterial species identified in the sinuses and those identified in the transplanted lungs of CF patients.^{9–11} Our study further supports the idea that the sinuses may serve as a source of allograft infection. The ability to differentiate between pre-transplant and post-transplant cultures from the lungs and sinuses offered an opportunity to determine if pre-existing sinus bacteria could colonize a lung allograft. We demonstrate that culturing PsA, MRSA, and *Burkholderia* in the sinuses prior to transplant correlated highly with the growth of the same pathogens in the lungs after transplant.

Our data show that colonization of the allograft often occurs rapidly (within one week), even in the setting of prophylactic antibiotics. Moreover, once the allograft was colonized, subsequent lung cultures tended to be positive regardless of recent antibiotic therapy. The reasons for this are unclear, but it is possible that the burden of infected debris in the sinuses of CF patients may be too high for systemic antibiotics and therefore produces a positive BAL. For the select patients who did not develop positive BAL cultures for several months or longer, it would be interesting to investigate in a future study whether treatment of CRS plays a role in preventing allograft colonization. So far, the results of clinical studies investigating this question are inconclusive. Holzmann et al. reported that a protocol involving surgery and daily irrigations decreased the rate of lower airway infection in lung transplant patients with CF.¹² Similarly, Vital et al. reported that post-transplant sinus surgery led to lower rates of pseudomonal airway colonization and improved survival.¹³ However, Leung et al. did not find a survival benefit with prophylactic pre-transplant sinus surgery.⁹

There are some limitations to this retrospective study. Given that lung allografts are from hosts without prior history of cystic fibrosis, the assumption was made that allografts were free of bacterial colonization. However, it is possible that nosocomial bacterial colonization can occur at the time of organ harvest or transplant. Additionally, we cannot exclude a secondary bacterial source elsewhere in the upper airway (i.e., pharynx, trachea) that can seed the allograft. Finally, we can only speculate on the clinical implications of allograft infection on our patient population, as we only examined raw culture data.

Conclusion

By examining the bacterial data obtained from pre-transplant sinuses and post-transplant BAL cultures, we affirm the hypothesis that pre-transplant sinus colonization is associated with post-transplant allograft colonization with the same pathogenic bacteria. Future

prospective studies are warranted to determine whether allograft function and longevity can be improved by aggressive management of sinusitis, even in the absence of symptoms.

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Table I**Demographics**

	Frequency
Total # of Transplants	n = 144
Male: Female	52:92
Mean Age at Transplant (range)	28.7 yo (13–62)
Mean Follow Up Duration	50 months
<i>Type of Lung Transplant</i>	
SOLT	1/144 (0.7%)
BOLT	143/144 (99.3%)
<i>Sinus Cultures</i>	
Pre-Transplant Culture	34/144 (23.6%)
Mean Duration from Culture to Transplant	7 months
Post-Transplant Culture	64/144 (44.4%)
Mean Duration from Transplant to Culture	15 months
<i>BAL Cultures</i>	
Pre-Transplant	139/144 (96.5%)
Post-Transplant	144/144 (100%)

SOLT = Single Orthotopic Lung Transplant; BOLT = Bilateral Orthotopic Lung Transplant;

Table II

Sinus Cultures

	Pre-Transplant (n=34)	Post Transplant (n=64)
<i>Pseudomonas</i>	21 (62%)	51 (80%)
MRSA	10 (29%)	22 (34%)
<i>Burkholderia</i>	3 (9%)	5 (8%)
<i>Achromobacter</i>	1 (3%)	5 (8%)
<i>Stenotrophomonas</i>	1 (3%)	3 (5%)
Other*	14 (41%)	33 (52%)
Fungus	4 (12%)	9 (14%)
<i>Mycobacteria</i>	0, 0%	2 (1%)
No bacteria	2 (6%)	1 (2%)

MRSA = Methicillin-resistant *Staphylococcus aureus*

* *Streptococci viridans*, Methicillin-Sensitive *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Haemophilus influenza*, and gram-negative rods

Table III

BAL Cultures

	Pre-Transplant (n=139)	Post Transplant (n=144)
<i>Pseudomonas</i>	93 (67%)	109 (76%)
MRSA	49 (35%)	57 (40%)
<i>Burkholderia</i>	20 (14%)	38 (26%)
<i>Achromobacter</i>	17 (12%)	17 (12%)
<i>Stenotrophomonas</i>	9 (6%)	37 (26%)
Other [*]	11 (8%)	19 (13%)
Fungus	47 (34%)	75 (52%)
<i>Mycobacteria</i>	77 (56%)	120 (83%)
No bacteria	3 (2%)	0 (0%)

BAL = Bronchoalveolar Lavage; MRSA = Methicillin-resistant *Staphylococcus aureus*

^{*} *Streptococci viridans*, Methicillin-Sensitive *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Haemophilus influenza*, and gram-negative rods.

Table IV

Correlation between Pre-Tx Sinus and Post-Tx BAL Cultures

	Pre-Tx Sinus	Post-Tx BAL	<i>p</i> - value
<i>Pseudomonas</i>	n = 21	n = 19/21	<i>p</i> = 0.003
MRSA	n = 10	n = 7/10	<i>p</i> = 0.013
<i>Burkholderia</i>	n = 3	n = 3/3	<i>p</i> = 0.001
<i>Achromobacter</i>	n = 1	n = 0/1	<i>p</i> = 0.696
<i>Stenotrophomas</i>	n = 1	n = 0/1	<i>p</i> = 0.548
Fungus	n = 4	n = 3/4	<i>p</i> = 0.650

Tx=Transplant; BAL=Bronchoalveolar Lavage; MRSA=Methicillin-Resistant *Staphylococcus aureus*

Table V

Correlation between Post-Tx Sinus and Post-Tx BAL Cultures

	Post-Tx Sinus	Post-Tx BAL	<i>p</i> - value
<i>Pseudomonas</i>	n = 24	n = 19/24	<i>p</i> = 0.031
MRSA	n = 10	n = 7/10	<i>p</i> = 0.014
<i>Burkholderia</i>	n = 3	n = 3/3	<i>p</i> = 0.001
<i>Achromobacter</i>	n = 2	n = 0/2	<i>p</i> = 0.722
<i>Stenotrophomas</i>	n = 1	n = 0/1	<i>p</i> = 0.142
Fungus	n = 4	n = 3/4	<i>p</i> = 0.458

Tx=Transplant; BAL=Bronchoalveolar Lavage; MRSA=Methicillin-Resistant *Staphylococcus aureus*

Table VI

Patients with Correlating Pre-Tx Sinus and Post-Tx BAL cultures

Patient	Pre-Transplant Sinus Culture	BAL 1wk	BAL 1mo	BAL 2mo	BAL 3mo	BAL 12mo
1	<i>B. cepacia</i>	n/a	+	+	+	+
2	<i>B. cepacia</i>	+	+	-	+	+
3	<i>B. cepacia</i>	-	+	+	+	+
4	MRSA	+	+	+	-	-
5	MRSA	-	-	n/a	+	n/a
6	MRSA	+	+	n/a	-	-
	PsA	+	+	n/a	+	+
7	MRSA	+	-	n/a	-	+
8	MRSA	n/a	-	n/a	-	-
9	MRSA	+	+	-	+	+
	PsA	+	+	-	+	+
10	MRSA	-	+	+	+	-
11	PsA	+	-	+	+	+
12	PsA	-	-	+	-	-
13	PsA	n/a	-	n/a	-	+
14	PsA	-	+	n/a	+	-
15	PsA	+	+	+	-	+
16	PsA	+	-	-	-	+
17	PsA	-	-	-	-	+
18	PsA	+	n/a	+	n/a	-
19	PsA	+	+	n/a	+	+
20	PsA	-	-	-	-	+
21	PsA	-	-	+	+	-
22	PsA	-	-	-	+	-
23	PsA	+	-	-	n/a	+

Patient	Pre-Transplant Sinus Culture	BAL 1wk	BAL 1mo	BAL 2mo	BAL 3mo	BAL 12mo
24	PsA	*** +	—	—	n/a **	+
25	PsA	*** —	— *	—	—	— *
26	PsA	+	— *	n/a **	n/a **	+
27	PsA	*** —	*** —	+	— *	+

Tx = Transplant; BAL = Bronchoalveolar Lavage; MRSA = Methicillin-resistant *Staphylococcus aureus*; PsA = *Pseudomonas aeruginosa*; n/a = culture data not available

* systemic antibiotic treatment for pneumonia

** systemic antibiotic treatment for other indications

+ positive BAL culture for corresponding Pre-Tx sinus culture

— negative BAL culture for corresponding Pre-Tx sinus culture