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RESPIRATORY INFECTIONS

Development of Chronic *Pseudomonas aeruginosa*-Positive Respiratory Cultures in Children with Tracheostomy

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Abstract

Background Up to 90% of children develop *Pseudomonas aeruginosa* (*Pa*)-positive respiratory cultures after tracheotomy.
Objective To identify the factors associated with chronic *Pa*-positive respiratory cultures in the first 2 years after tracheotomy.
Methods We conducted a retrospective cohort study of 210 children ≤ 18 years old who underwent tracheotomy at a single freestanding children's hospital that had two or more years of respiratory cultures post-tracheotomy available for analysis. We conducted multivariable logistic regression to test the association between demographic and clinical factors to our primary outcome of chronic *Pa* infection, defined as > 75% of respiratory cultures positive for *Pa* in the first 2 years after tracheotomy.
Results Of the primarily male (61%), Hispanic (68%), and publicly insured (88%) cohort, 18% ($n = 37$) developed chronic *Pa*-positive respiratory cultures in the first 2 years. On multivariable logistic regression, pre-tracheotomy *Pa*-positive respiratory culture (aOR 11.3; 95% CI 4–1.5) and discharge on beta agonist (aOR 6.3; 95% CI 1.1–36.8) were independently associated with chronic *Pa*-positive respiratory cultures, while discharge on chronic mechanical ventilation was associated with decreased odds (aOR 0.3; 95% CI 0.1–0.7). On sensitivity analysis examining those without a pre-tracheotomy *Pa*-positive respiratory culture, discharge on MV continued to be associated with decreased odds of chronic Pa (aOR 0.1; 95% CI 0.02–0.4) and three other variables (male gender, chronic lung disease, and discharge on inhaled corticosteroids) were associated with increased odds of chronic *Pa.*
Conclusion Because pre-tracheotomy *Pa* growth on respiratory culture is associated with post-tracheotomy chronic *Pa*-positive respiratory cultures, future research should examine pre-tracheotomy *Pa* eradication or suppression protocols.

Keywords Tracheitis · Pneumonia · bacterial · Tracheostomy · Pediatric · *Pseudomonas aeruginosa*

Introduction

Bacterial pneumonia and other respiratory tract infections are common reasons for hospitalizations in children with pre-existing tracheostomy [1–4]. Bacterial colonization after tracheostomy placement is nearly universal [5], with up to 90% of children having respiratory cultures that grow *Pseudomonas aeruginosa* (*Pa*) at some point post-tracheotomy [6]. While poor clinical outcomes due to *Pa* acquisition in children with cystic fibrosis (CF) are well established, fewer studies have examined the association between the *Pa* growth from tracheal aspirates and clinical outcomes in children with tracheostomy. Previous studies have shown an association between *Pa* recovery on respiratory culture, chronic aspiration, and hospitalization for pneumonia in children with medical complexity (CMC) [7, 8]. With respect to children with tracheostomy, one prospective study of 45 children undergoing tracheotomy describes the timing

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of *Pa* lower airway colonization and found that *Pa* airway colonization often began with oropharyngeal carriage pre-tracheostomy that progressed to endotracheal tube and the subsequent tracheostomy tube and lower airways colonization [9]. *Pa* recovery has also been associated with respiratory infection readmission in children with tracheostomy [10]. Given the associations between chronic *Pa* infection and pulmonary exacerbations in patients with CF [11, 12], the high rates of *Pa* recovery in children with tracheostomy, and the morbidity associated with *Pa* in CMC, it may be important to identify children with pre-existing tracheostomy at an increased risk for chronic *Pa*-positive respiratory cultures. Therefore, the objective of the current study is to identify the factors associated with chronic *Pa*-positive respiratory cultures in the first 2 years after tracheotomy. We hypothesized that having a *Pa*-positive respiratory culture before tracheotomy would be associated with increased odds of chronic *Pa* after tracheotomy.

Methods

Study Population

We conducted a single-center retrospective cohort study of pediatric patients who underwent tracheotomy at Children's Hospital Los Angeles (CHLA), a university-based children's hospital. Using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM)* procedure code for tracheotomy previously used in studies for examining pediatric tracheotomy (*ICD-9-CM*: 31.1, 31.2, 31.21, 31.29) [13, 14], we identified all patients between 0–18 years of age who were discharged from the hospital with tracheostomy between 1/1/2005 and 6/30/13 with at least 2 years of respiratory cultures recorded after tracheostomy placement. For context, *Pa* is the dominant organism at our center for children with tracheostomy, with nearly 75% of children growing *Pa* at some point after tracheotomy.

Primary Predictor

Our primary predictor of interest was the presence or absence of a *Pa*-positive respiratory culture prior to tracheotomy.

Primary Outcome

Our primary outcome was the development of chronic *Pa*-positive respiratory cultures, defined as ≥ 75% *Pa*-positive cultures during the first 2 years after tracheotomy. This definition has been used in previous studies of cystic fibrosis [15].

Covariates

Covariates from the initial hospitalization when tracheostomy occurred were gathered by a combination of medical chart review and via administrative data gathered from the Pediatric Health Information Systems (PHIS) database which contains de-identified inpatient, emergency room, ambulatory surgery, and observation unit data from 48 free-standing children's hospitals [16]. Covariates included: (1) Demographic data (e.g., gender, race/ethnicity, insurance, prematurity (defined as gestational age < 37 weeks); (2) clinical variables during the index hospitalization when tracheotomy occurred (e.g., age at tracheotomy, LOS), medical comorbidities associated with tracheotomy, including upper airway obstruction (e.g., vocal cord paralysis), chronic lung disease (e.g., bronchopulmonary dysplasia), and neuromuscular disease (e.g., spinal muscular atrophy, spastic quadriplegia), and trauma [14, 17]; and (3) post-tracheotomy discharge details including discharge on home with positive pressure ventilation and discharge medications (e.g., respiratory, gastrointestinal).

Statistical Methodology

We used descriptive statistics and bivariate analyses to test the association between our primary predictor variable and covariates with development of chronic *Pa* infection. Bivariate logistic (for binary predictors) and linear regressions (for continuous predictors) are reported through unadjusted odds ratios (uOR) with 95% confidence intervals (CI). The primary predictor and all covariates were entered into the multivariable logistic regression, for which we report adjusted odds ratios (aOR) with 95% CI. All models were analyzed using SPSS Statistics for Windows version 23. The study was reviewed by the Children's Hospital Los Angeles Institutional Review Board and was approved with waiver of consent as per 45 CFR 46.110/21 CFR 56.110.

Results

A total of 210 patients who underwent tracheotomy during the study period met study inclusion criteria (Table 1). The cohort was 61% ($n = 127$) male, 68% ($n = 142$) Hispanic, and 88% ($n = 184$) on public insurance. With respect to the index hospitalization where tracheotomy occurred, median age at tracheotomy was 7 months [interquartile range (IQR) 4–46 months] and median pre-tracheotomy length of stay was 34 days (IQR 16–61 days). Comorbidities associated with tracheotomy indication included prematurity (33%; $n = 70$), upper airway obstruction (35%; $n = 74$), chronic

Table 1 Univariate and multivariable logistic regression model of factors associated with development of chronic *Pseudomonas aeruginosa*-positive respiratory cultures during the first 2 years after tracheotomy

Variable	Total $N=210$	Unadjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Demographics					
Male	127 (61%)	2.0 (0.9, 4.3)	0.09	1.9 (0.8, 5)	0.17
Age at tracheotomy (in years)		1 (0.96,1.1)	0.49	1.01 (0.92, 1.1)	0.81
Public Insurance	184 (88%)	6.1 (0.8, 46.4)	0.08	5.3 (0.6, 47.1)	0.13
Race/ethnicity					
Hispanic	142 (68%)	Ref		Ref	
Non-Hispanic White	20 (10%)	0.7 (0.2–2.6)	0.62	0.9 (0.2, 4.4)	0.92
Non-Hispanic Black	24 (11%)	0.4 (0.1–1.7)	0.2	0.4 (0.1–2.7)	0.36
Non-Hispanic Other	24 (11%)	0.8 (0.3–2.6)	0.73	1.9 (0.4–8.1)	0.41
Selected comorbidities associated with tracheotomy					
Prematurity (<37 weeks gestational age)	70 (34%)	0.8 (0.4–1.7)	0.56	0.7 (0.2–1.9)	0.44
Upper airway obstruction/vascular anomaly	74 (35%)	0.9 (0.4–1.8)	0.69	1.0 (0.4–2.8)	0.98
Chronic lung disease	127 (61%)	1.3 (0.6–2.6)	0.55	1.6 (0.6–4.1)	0.36
Neuromuscular disease	117 (56%)	1.2 (0.6–2.5)	0.61	0.8 (0.3–2)	0.59
Trauma	9 (4%)	0.6 (0.1–4.7)	0.61	–	–
Discharge Medications					
Discharged on bronchodilators	174 (83%)	4.3 (1.0, 18.7)	0.05	6.0 (1.02–35.1)	0.048
Discharged on inhaled corticosteroids	118 (56%)	1.8 (0.9, 3.8)	0.13	1.9 (0.7–5.2)	0.24
Discharged on ipratroprium	39 (19%)	1.0 (0.4–2.6)	0.95	0.4 (0.1–1.5)	0.19
Discharged on GI acid suppression	132 (63%)	0.6 (0.3–1.3)	0.64	0.5 (0.2–1.4)	0.19
Discharged on GI pro-motility agents	76 (36%)	0.6 (0.3–1.3)	0.2	1.1 (0.4–2.9)	0.92
Discharged on mechanical ventilation	111 (53%)	0.6 (0.3–1.1)	0.10	0.3 (0.1 to 0.7)	0.005
Total number of post-tracheostomy cultures taken in the 2-year study period	–	1.07 (1.01–1.13)	0.02	1.03 (0.96 to 1.1)	0.46
Pre-tracheotomy Pa-positive respiratory culture	38 (18%)	6.2 (2.8, 13.6)	<0.001	10.6 (3.7, 30.0)	<0.001

lung disease (60%; $n=127$), and neuromuscular disease (56%; $n=117$). For our primary predictor, 18% ($n=38$) had a positive respiratory culture for *Pa* prior to tracheotomy, with a median of 135 days [IQR 1–380] between first *Pa*-positive respiratory culture and tracheotomy. With respect to immediate post-tracheotomy discharge characteristics, over half ($n=111$) were discharged on chronic mechanical ventilation. Most patients were discharged on inhaled bronchodilators and corticosteroids, with fewer than 20% receiving ipratropium. Nearly 63% ($n=132$) were discharged on gastrointestinal acid suppression (e.g., proton-pump inhibitors, histamine-2-recepteo blockers) and 36% ($n=76$) were discharged on gastrointestinal pro-motility agents (e.g., metoclopramide, erythromycin). Only three patients in the cohort received inhaled tobramycin on post-tracheotomy hospital discharge.

In the first 2 years after tracheotomy, the median number of respiratory cultures obtained was 6 (IQR 3–10). With respect to our primary outcome, 17.6% ($n=37$) developed chronic *Pa*-positive respiratory cultures during the follow-up period. Those who developed chronic *Pa* had higher number of respiratory cultures in the follow-up period compared to those without chronic *Pa* (median = 8 vs 5; $p=0.02$). We found that 11 children with a positive *Pa* culture prior to tracheotomy did not grow *Pa* in the 2 years after tracheotomy; this group had a median of 5 (IQR 4–7) respiratory cultures completed during the study period.

On unadjusted logistic regression, a pre-tracheotomy *Pa*-positive respiratory culture (uOR = 6.2; 95% CI: 2.8–13.6) and increasing number of cultures during the study period (uOR = 1.07; 95% CI: 1.01–1.13) were associated with increased odds of chronic *Pa* development. On multivariable logistic regression, a pre-tracheotomy *Pa*-positive respiratory culture continued to be independently associated with increased odds of chronic *Pa* development (aOR 10.6; 95% CI: 3.7–30). Discharge on inhaled beta agonists was associated with increased odds of chronic *Pa* (aOR 6; 95% CI: 1.01–35.1). The only variable associated with decreased odds of chronic *Pa* development was discharge on mechanical ventilation (aOR 0.3; 95% CI: 0.1–0.7). No other variables included reached statistical significance on multivariable modeling.

We conducted a post hoc subgroup analysis examining the association between demographic and clinical factors

and odds of chronic *Pa* cultures in the 2 years after initial tracheostomy placement for patients without a history of pre-tracheostomy *Pa* infection (Table 2). In this subgroup, *Pa*-positive cultures developed at a median of 297 days [IQR 116, 623] after tracheotomy. In the subgroup analysis, discharge on MV continued to be associated with decreased odds of chronic *Pa* (aOR 0.1; 95% CI: 0.02–0.4). Additionally, male gender (aOR 5.4; 95% CI: 1.3–22.5), chronic lung disease (aOR 4.8; 95% CI: 1.03–22.5), and discharge on inhaled corticosteroids (aOR 15.8; 95% CI: 1.6–157.3) were found to be associated with increased odds of chronic *Pa* development, while the association between bronchodilators and chronic *Pa* became non-significant.

Discussion

In this single-center study of 210 patients undergoing tracheotomy with 2 years of respiratory cultures, we found that only 18% of pediatric patients developed chronic *Pa*-positive respiratory cultures in the first 2 years after tracheostomy. This rate of chronic *Pa*-positive cultures is similar to the 17% seen in patients with cystic fibrosis [15]. A pre-tracheotomy *Pa*-positive respiratory culture and discharge on inhaled bronchodilators were associated with increased odds of development of chronic *Pa*-positive respiratory cultures, while discharge on mechanical ventilation was associated with lower odds of chronic *Pa*.

Higher rates of post-tracheotomy chronic *Pa*-positive respiratory cultures complements prior research showing associations between oropharyngeal *Pa* colonization and subsequent lower airway colonization [9] and associations between a history of *Pa*-positive cultures and subsequent *Pa* respiratory tract infection readmissions in children with tracheostomy [10] and in children with medical complexity hospitalized with pneumonia [7, 8]. The relationship between bronchodilators and increased odds of *Pa* warrants further investigation. This may be because discharge on beta agonists is a marker of overall illness severity rather than a specific biological relationship between beta agonists and *Pa*. Indeed, this association was not found in patients without history of pre-tracheostomy *Pa* infection. Several in vitro studies have demonstrated that beta agonists are protective of *Pa*-induced [18–20] and other bacteria-induced [21, 22] airway epithelium damage. However, one study demonstrated an association between beta agonists and an

Table 2 Univariate and multivariable logistic regression model of factors associated with development of chronic *Pseudomonas aeruginosa*-positive respiratory cultures during the first 2 years after tracheotomy for patients *without* a history of pre-tracheostomy *Pa*

Variable	Total $N=169$	Unadjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Demographics					
Male	101 (60%)	3 (0.96–9.4)	0.06	5.4 (1.3, 22.5)	0.02
Age at tracheotomy (in years)	–	1.04 (0.95–1.14)	0.35	1.1 (0.99, 1.3)	0.07
Public insurance	148 (88%)	2.9 (0.4–23.2)	0.31	4.5 (0.3, 60,1)	0.26
Race/ethnicity					
Hispanic	113 (67%)	REF	–	REF	
Non-Hispanic White	15 (9%)	0.5 (0.06–3.8)	0.48	0.3 (0.02–8.2)	0.51
Non-Hispanic Black	19 (11%)	0.4 (0.05–2.9)	0.34	0.8 (0.07, 7.9)	0.82
Non-Hispanic other	22 (13%)	1.03 (0.3–3.9)	0.96	5.4 (0.7, 39.1)	0.10
Selected comorbidities associated with tracheotomy					
Prematurity (<37 weeks gestational age)	56 (33%)	0.6 (0.2–1.9)	0.41	0.5 (0.11, 1.8)	0.27
Upper airway obstruction/vascular anomaly	64 (38%)	1.1 (0.4–2.9)	0.83	0.5 (0.1, 2.1)	0.33
Chronic lung disease	105 (62%)	2 (0.7–5.7)	0.21	4.8 (1.03, 22.5)	0.046
Neuromuscular disease	91 (54%)	1.05 (0.4–2.7)	0.91	0.6 (0.2, 2.1)	0.47
Trauma	9 (5%)	–	–	–	–
Discharge medications					
Discharged on bronchodilators	138 (82%)	2.2 (0.5–9.9)	0.32	0.8 (0.1, 10.7)	0.85
Discharged on inhaled corticosteroids	96 (57%)	5 (1.4–17.9)	0.01	15.8 (1.6, 157.3)	0.02
Discharged on ipratroprium	29 (17%)	0.8 (0.2–3.1)	0.79	0.21 (0.04, 1.2)	0.09
Discharged on GI acid suppression	101 (60%)	0.5 (0.2–1.3)	0.16	1 (0.3, 3.9)	1.00
Discharged on GI pro-motility agents	66 (39%)	0.5 (0.2–1.4)	0.18	0.78 (0.2, 3)	0.72
Discharged on mechanical ventilation	86 (51%)	0.3 (0.1–0.8)	0.02	0.1 (0.02, 0.4)	0.002
Total number of post-tracheostomy cultures taken in the 2-year study period	–	1.03 (0.96–1.11)	0.36	1.03 (0.94, 1.1)	0.51

impaired clearance of *Haemophilus influenzae* [23], suggesting a potential mechanism of persistence of positive *Pa* cultures in our population.

The findings associated with lower odds of chronic *Pa* infection in children discharged on mechanical ventilators complements previous studies showing lower odds of readmission for bacterial respiratory infections [4, 10]. This finding may be due to the decreased exposure to environmental pathogens that the closed system of a ventilator provides, greater focus on airway clearance in the ventilated population, or decreased atelectasis. Given the complexity of care needed to live outside of the hospital on mechanical ventilation, they may also be more likely to live in chronic care facilities, which may confer differential risk of chronic *Pa* development.

Our exploratory subgroup analysis of patients without a pre-tracheostomy *Pa*-positive cultures provide results that warrant further consideration in larger, prospective trials. In this group, we found that male gender, chronic lung disease, and discharge on inhaled corticosteroids were all independently associated with higher odds of chronic *Pa* development, while discharge on mechanical ventilation continued to be associated with decreased odds. Our findings of associations between chronic lung disease and higher odds of chronic *Pa* respiratory culture likely reflects overall severity of lung disease and poorer airway clearance. Similarly, the association between inhaled corticosteroids and development of chronic *Pa* may reflect overall severity of lung disease or local tissue immune suppression from the corticosteroids. While our previous work found no association between inhaled corticosteroids and hospital readmission for a bacterial tracheostomy-associated infection [10], our finding of an association between inhaled corticosteroids and increased odds of chronic *Pa* is in line with some adult studies that have demonstrated associations between inhaled corticosteroids and pneumonia in observational studies. In review of two meta-analyses looking at inhaled corticosteroids and pneumonia risk in adults with asthma and COPD, while inhaled corticosteroids were associated with increased incidence of pneumonia on unadjusted analysis of observational trials, in meta-analyses of randomized controlled trials, inhaled corticosteroids were associated with decreased rates of pneumonia (for asthma) [24] and similar rates of pneumonia fatality/overall mortality (for COPD) [25]. Similar findings have been found in meta-analysis of RCTs studying children with asthma taking inhaled corticosteroids [26]. Further exploration of the associations between inhaled corticosteroids and chronic *Pa* development is needed, given that nearly 60% of our patients received inhaled corticosteroids on discharge.

The current study had several strengths. We had detailed patient data from the chart review of over 200 pediatric patients with post-tracheotomy follow-up for at least 2 years and a high median number of respiratory cultures. The study was not without its limitations. First, because this is a retrospective study, there are unmeasured variables, such as place of residence after hospital discharge, which may have confounded test results. For example, for non-ventilated patients, we did not gather data regarding the use of tracheostomy collars, heat moisture exchangers, tracheostomy caps, or other devices, that may affect differential rates of chronic *Pa* development as closed-circuit ventilators do. We do not have culture results from clinics or hospitals outside of our center; therefore, we may have misclassified participant *Pa* chronicity because of incomplete information. However, given our large home mechanical ventilation program and our care model for children with tracheostomy, we believe that most of these patients had their testing done at our center. Although we collected pre-tracheotomy respiratory culture results, unlike a previous study [9], we do not have oropharyngeal respiratory culture results prior to tracheotomy. During the study period, there was no standardized policy to obtain surveillance tracheostomy cultures; thus, cultures were done at the discretion of the ordering provider and we did not correlate these test results with other markers of acute infection such as respiratory tract infection symptoms or other laboratory test results. Thus, we cannot examine whether having early, chronic *Pa*-positive cultures was associated with differential outcomes. Importantly, we did not correlate chronic *Pa* infection with viral infection or prior antibiotic exposure, both of which change the quantity and type of bacteria present in the tracheal microbiome [27, 28]. Finally, unlike CF, respiratory cultures were not done at regular intervals, so there are consistencies in the number and timing of samples.

Not withstanding these limitations, our study has detailed patient data from chart review of over 200 children with post-tracheotomy follow-up for at least 2 years and a high median number of respiratory cultures. Fewer than 20% of patients developed chronic *Pa*, and pre-tracheotomy *Pa*-positive respiratory culture was strongly associated with chronic *Pa*-positive respiratory cultures. Given that 70% of children with suspected tracheostomy-associated respiratory infections received empiric *Pa*-targeted antibiotics [2, 29], the low rates of chronic *Pa*-positive respiratory cultures identified in this study suggest that empiric *Pa*-targeted antibiotic therapy may not always be needed. Future research should examine the association between chronic *Pa* and clinical outcomes such as hospital readmissions and illness severity. Previous studies have shown associations between *Pa* recovery and poorer outcomes in this population [10]. While one previous published study has shown some benefit with using topical antibiotics to decrease airway colonization in children with tracheostomy [30], future research may also examine *Pa* eradication or suppression protocols (e.g.,

inhaled or topical antibiotics) to decease respiratory-related morbidity in children with tracheostomy.

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Author contributions Dr. Russell conceptualized and designed the study, conducted the statistical analyses, drafted the initial manuscript, and approved the final manuscript as submitted. Drs. Simon and Neely assisted in study design, reviewed and critically revised the manuscript, and approved the final manuscript as submitted.

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Compliance with Ethical Standards

Conflict of interest: The authors have no conflicts of interest relevant to this article to disclose.

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