Respiratory Culture Growth and 3-Year Lung Health Outcomes in Children with BPD and Tracheostomies

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Abstract

Background: While bacteria identification on respiratory cultures is associated with poor short-term outcomes in children with bronchopulmonary dysplasia (BPD) and tracheostomies, the influence on longer-term respiratory support needs remains unknown. **Objective:** To determine if respiratory culture growth of pathogenic organisms is associated with ongoing need for respiratory support, decannulation, and death at 3 years post-tracheostomy placement in children with BPD and tracheostomies. **Methods:** This single center, retrospective cohort study included infants and children with BPD and tracheostomies placed 2010-2018 and >1 respiratory culture obtained in 36 months post-tracheostomy. Primary predictor was any pathogen identified on respiratory culture. Additional predictors were any *Pseudomonas aeruginosa* and chronic *P. aeruginosa* identification. Outcomes included continued use of respiratory support (e.g., oxygen, positive pressure), decannulation, and death at 3 years post-tracheostomy. We used Poisson regression models to examine the relationship between respiratory organisms and outcomes, controlling for patient-level covariates and within-patient clustering. **Results:** Among 170 children, 59.4% had a pathogen identified, 28.8% ever had *P. aeruginosa*, and 3.5% had chronic *P. aeruginosa*. At 3 years, 33.1% of alive children required ongoing respiratory support and 24.8% achieved decannulation; 18.9% were deceased. In adjusted analysis, any pathogen and *P. aeruginosa* were not associated with ongoing respiratory support or mortality. However, *P. aeruginosa* was associated with decreased risk of decannulation (aRR 0.48, 95% CI 0.23-0.98). Chronic *P. aeruginosa* was associated with lower survival probability. **Conclusion**: Our findings suggest that respiratory pathogens including *P. aeruginosa* may not promote long-term respiratory dysfunction, but identification of *P. aeruginosa* may delay decannulation.

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This article includes original research. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board as exempt research.

This article does not include images of people .

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Abbreviations : ARI, acute respiratory infection; BPD, bronchopulmonary dysplasia; CLDI, chronic lung disease of infancy; CCC, complex chronic condition; CCHMC, Cincinnati Children's Hospital Medical Center; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EMR: electronic medical record; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IQR: interquartile range; RR, risk ratio, aRR, adjusted risk ratio.

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Contributors' Statement

Dr. Steuart contributed to the conceptualization and design the study, performed data collection, assisted with data analysis and validation, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content.

Dr. Pan conceptualized and designed the study, performed data analysis and validation, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content.

Drs. Thomson and Benscoter conceptualized and designed the study, coordinated and supervised data collection, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content.

Ms. Woolums assisted with data analysis and validation, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content.

Drs. Russell and Henningfeld assisted with data analysis and validation, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Background: While bacteria identification on respiratory cultures is associated with poor short-term outcomes in children with bronchopulmonary dysplasia (BPD) and tracheostomies, the influence on longer-term respiratory support needs remains unknown.

Objective: To determine if respiratory culture growth of pathogenic organisms is associated with ongoing need for respiratory support, decannulation, and death at 3 years post-tracheostomy placement in children with BPD and tracheostomies.

Methods: This single center, retrospective cohort study included infants and children with BPD and tracheostomies placed 2010-2018 and > 1 respiratory culture obtained in 36 months post-tracheostomy. Primary predictor was any pathogen identified on respiratory culture. Additional predictors were any *Pseudomonas aeruginosa* and chronic *P. aeruginosa* identification. Outcomes included continued use of respiratory support (e.g., oxygen, positive pressure), decannulation, and death at 3 years post-tracheostomy. We used Poisson regression models to examine the relationship between respiratory organisms and outcomes, controlling for patient-level covariates and within-patient clustering.

Results: Among 170 children, 59.4% had a pathogen identified, 28.8% ever had *P. aeruginosa* , and 3.5% had chronic *P. aeruginosa* . At 3 years, 33.1% of alive children required ongoing respiratory support and 24.8% achieved decannulation; 18.9% were deceased. In adjusted analysis, any pathogen and *P. aeruginosa*were not associated with ongoing respiratory support or mortality. However, *P. aeruginosa* was associated with decreased risk of decannulation (aRR 0.48, 95% CI 0.23-0.98). Chronic *P. aeruginosa* was associated with lower survival probability.

Conclusion : Our findings suggest that respiratory pathogens including *P. aeruginosa* may not promote long-term respiratory dysfunction, but identification of *P. aeruginosa* may delay decannulation.

Introduction

Following tracheostomy placement, infants and children with bronchopulmonary dysplasia (BPD) and tracheostomies are a vulnerable population. This group has twice the risk of rehospitalization as infants without BPD, predominantly for respiratory infections,[1,2] and a mortality rate of 11-20% by 2 years of age.[1,3,4] Among young children with BPD, the expected respiratory course is one of improvement in lung function with time and alveolar growth.[5] For those who require tracheostomy placement for chronic respiratory support, the weaning of support is widely viewed as a sign of improving pulmonary function, with liberation from ventilation generally expected by 24-30 months.[6-9] Subsequent decannulation is also anticipated, and is viewed as a sign of airway growth and patency and respiratory stability. However, only one-third to half of children with BPD and tracheostomies follow this trajectory of lung health improvement.[1,3,6-8,10-12] The reasons why other children are unable to achieve improved lung health are unclear.

Identification of pathogenic bacteria during respiratory culture testing is common among children with tracheostomies. We hypothesize that respiratory bacteria, whether acute infectious or chronically colonizing bacteria, may influence prolonged tracheostomy dependence and mortality. Identification of *Pseudomonas aeruginosa* in the respiratory tract of children with tracheostomies has been associated with increased risk of re-hospitalization for respiratory infection.[13]Respiratory tract colonization with *P. aeruginosa* and other bacteria are well-defined entities and well-documented causes of lung function decline in children and adults with cystic fibrosis.[14-18] Although long-term colonization has not been defined in children with tracheostomies, recurrent *P. aeruginosa* isolation on tracheostomy aspirate cultures has been associated with poor short-term outcomes, including longer hospitalizations and higher readmission rates.[13,19]However, long term outcomes of acute and recurrent bacterial isolation have not been assessed among children with tracheostomies or those with BPD.

In this study of children with BPD and tracheostomies, we sought to assess the association of respiratory culture organism isolation, particularly *P. aeruginosa* , and lung health outcomes at 3 years post-tracheostomy placement, including ongoing need for respiratory support, delayed decannulation, and death. We hypothesized that children with *P. aeruginosa* bacterial identification would have higher likelihood of each poor outcome compared with children who did not have such bacterial isolation.

Methods

Study Design, Patient Population, and Data Source

This single-center, retrospective cohort study included children with BPD and tracheostomies cared for at Cincinnati Children's Hospital Medical Center (CCHMC) between January 2010 and December 2018. The study population was identified using existing internal tracheostomy and BPD registries; BPD diagnosis was additionally verified by the presence of relevant International Classification of Diseases diagnosis codes for BPD or chronic lung disease of infancy (BPD: *ICD* -9 770.7,*ICD* -10 P27.1, CLDI: ICD-9 770.7, *ICD* -10 P27.8). Inclusion criteria required at least 1 bacterial respiratory culture (tracheostomy aspirate or bronchoalveolar lavage) obtained in the 3 years following tracheostomy placement. Children with cystic fibrosis and those without follow-up data at 3 years were excluded. Detailed demographic, clinical, respiratory culture, and respiratory support data for all encounters were obtained from the electronic medical record (EMR). Culture data included details of Gram stain, semi-quantitative organism results, and specimen source. Dates of tracheostomy placement, and, if applicable, dates of death were also obtained. This study was approved by the CCHMC Institutional Review Board as exempt research.

Predictors and Outcomes

We determined 3 predictor groups based on dichotomous bacterial identification. Inpatient, outpatient, and laboratory-collected cultures were included to define these categories. The group of children with "any pathogen identified" was defined as those with identification of at least 1 pathogenic organism on any respiratory culture obtained in the first 3 years following tracheostomy placement (inclusive of*P. aeruginosa,* **Figure 1a**). The group of "any *P. aeruginosa* identified" was defined as children with identification of*P. aeruginosa* specifically on at least one respiratory culture in this timeframe. The group of "chronic *P. aeruginosa* identified" was defined as the subgroup of children with isolation of *P. aeruginosa* in $> 50\%$ of cultures obtained in any continuous 12-month period in the 3 years post-tracheostomy placement using an adaptation to previously-described criteria.[20] To evaluate the effect of repeated organism growth events, each child's count of cultures with pathogenic organisms and count of cultures with *P. aeruginosa* during the 3 years of enrollment post-tracheostomy were summarized as additional predictor variables.

"Pathogenic organisms" were defined *a priori* according to CCHMC microbiology lab guidelines as organism types and quantities not expected in oropharyngeal flora, including but not limited to*Pseudomonas aeruginosa, Staphylococcus aureus,* and*Klebsiella pneumoniae,* as previously described.[21] Cultures with no speciated organisms or only "oropharyngeal flora" were categorized as "negative". The CCHMC microbiology lab defines oropharyngeal flora broadly, to include*Haemophilus* species, *Streptococcus pneumoniae* ,*Staphylococcus aureus* , and *Moraxella catarrhalis* when isolated in small numbers with other oropharyngeal flora. This microbiology lab does not have specimen rejection criteria.

The primary outcome was the alive child's continued use of respiratory support at 3 years post-tracheostomy placement. Respiratory support use was defined dichotomously as the use of any of the following: supplemental oxygen, high flow nasal cannula, continuous positive airway pressure(CPAP), bilevel positive airway pressure(BiPAP), or mechanical ventilation at baseline when well for any portion of the day or night. Secondary outcomes examined were decannulation status at 3 years post-tracheostomy placement and death by 3 years post-placement.

Covariates

Demographic and patient characteristics that might influence 3-year respiratory support needs, decannulation, and death were obtained from the EMR including age, sex, race, ethnicity, insurance type, comorbid

diagnoses, and home ventilator use. Sex, race, and ethnicity were included as covariates to describe the population and were not treated as biologic constructs. Encounter-level diagnoses were pooled across each child's encounters over time and coded to identify complex chronic conditions (CCCs) using previously-defined ICD-9 and -10 codes.[22] Home ventilator use was defined at the time of first Pulmonary visit after hospital discharge as the requirement, when well, for mechanical ventilation for any portion of the day/night and for any duration after initial discharge with tracheostomy until 3 years after placement. Initial hospital discharge typically occurs several months after tracheostomy placement at our institution.

Statistical analysis

Continuous variables were described using medians and interquartile ranges (IQR). Categorical variables were described using counts and percentages. Patient characteristics and outcomes were stratified by primary exposure and compared using Chi-square test or Fisher's exact test for categorical variables as appropriate and Wilcoxon rank sum test for continuous variables. Generalized linear models were used for comparisons in child-level count data while generalized linear mixed models were used for comparisons in culture-level data to account for the correlation within child clusters.

Poisson regression models with robust standard errors were used to examine the association between each predictor group (of dichotomous culture status) and children's 3-year outcomes, adjusted for covariates including sex, race, insurance type, and number of complex chronic conditions and accounting for correlation within child clusters. Kaplan-Meier survival analyses with log-rank test were used to assess death-free survival. Race was included in analysis due to known racial differences in outcomes among infants with BPD,[23] and as a proxy for structural racism and bias.

Analyses were performed with SAS V9.4 (SAS Institute Inc., Cary, NC, USA) and with R v4.1.1 (Vienna, Austria).[24] P -values <0.05 were considered statistically significant.

Results

Study Cohort

Among 170 children with BPD and tracheostomies included during the 9-year study period, 2,103 bacterial respiratory cultures were obtained (median 10 cultures per child over their 3 years of enrollment, IQR:3-17, full range 1-45, **Table 1**). Children had a median age at tracheostomy placement of 4.1 months (IQR: 3.2-5.3 months). Children had a median 5 CCCs per child (IQR: 4-6) and 67.6% required baseline chronic ventilator use at some point in their 3 years post-tracheostomy.

Over half (59.4%) of children had any pathogen identified on bacterial isolation on respiratory cultures during the 3-years post-tracheostomy (**Table 1, Figure 1**). Among children with pathogens identified, the median time to first pathogen post-tracheostomy placement was 3.7 months (IQR: 0.9-11.5 months). Among children with any *P. aeruginosa* , the median time to first *P. aeruginosa*post-tracheostomy placement was 3.3 months (IQR: 0.8-11.2 months).

Compared with children who never had pathogens identified, children with any pathogen identification were more likely to be privately insured (45.5% vs. 23.2%, p=0.003), but there were no differences in gender, race, or ethnicity. Children with pathogen identification had more CCCs (median 5 CCCs [IQR: 4-6] vs. 4 CCCs [IQR: 3-6], p=0.04) and were also more likely to use a ventilator at baseline (74.3% vs. 58.0%, p=0.03). Children with pathogen identification had approximately three times more cultures collected per child compared with children without pathogen identification (median 12 [IQR: 7-18] vs. 4 [IQR: 2-13], p<0.001).

Respiratory Cultures

A minority of cultures (13.4%) had isolation of one or more pathogenic respiratory organisms (**Table 2**). Compared with nonpathogenic culture results, cultures with pathogen identification were more likely collected among younger children (median age at culture 0.7 years vs 1.3 years, p<0.001) and children with a concurrent ICD-9 or ICD-10 diagnosis of ARI during the specified encounter (45.7% vs. 31.6%, p<0.001).

Cultures with pathogens were more frequently of tracheostomy aspirate source than bronchoalveolar lavage (87.2% vs 63.0%, p<0.001).

Overall, 22 pathogenic organism species were identified in respiratory cultures from this population. The most frequent pathogens identified were *P. aeruginosa* and *S. aureus,* which were identified in 5.1% and 4.7% of all cultures respectively (**Table 2**).

Predictor Groups

Among the 101 children (59.4%) who had any pathogen identified on respiratory culture during the 3 years post-tracheostomy, 48.5% had any*P. aeruginosa* identified specifically (**Figure 1a**). Six children met criteria for chronic *P. aeruginosa* identification (12.2% of *P. aeruginosa* group and 3.5% of the entire cohort).

Children with pathogens identified had median of 2 cultures with pathogens (IQR: 1-3, range 1-27) during the 3 years post-tracheostomy; those with *P. aeruginosa* identified had median of 1 culture identifying *P. aeruginosa* (IQR: 1-2, range 1-6).

3-Year Outcomes

At 36 months post-tracheostomy placement, 44 children (26.8% of all children; 33.1% of alive children) were still using respiratory support and 100 children (61.0% of all children; 75.2% of alive children) were still cannulated with their tracheostomy (**Figure 1b** ,**Table 3**). Nearly one-fifth (18.9%) of children died within 3 years post-tracheostomy. Six children were lost to follow up by 3 years post-tracheostomy; these children were lost to follow up at median 8.9 months post-tracheostomy (IQR: 7.6-11.3 months).

In unadjusted analysis, fewer children with *P. aeruginosa*identification were decannulated at 3 years post-tracheostomy as compared with children without *P. aeruginosa* (18.2% vs. 35.0%, p=0.07, **Table 3**) though this difference did not reach statistical significance. No differences in respiratory support, decannulation, or mortality outcomes were identified for children with any pathogen identification vs. no pathogen identification or for children with chronic *P. aeruginosa* identification vs. no chronic identification.

In adjusted analysis, having any *P. aeruginosa* identification was associated with lower probability of decannulation by 3 years post-tracheostomy (adjusted risk ratio [aRR] 0.48, 95% confidence interval [95% CI] 0.23-0.98, **Figure 2**). Furthermore, when analyzing count of *P. aeruginosa* isolations during the timeframe, each identification of *P. aeruginosa* was associated with a 35% lower probability of achieving decannulation by 3 years post-tracheostomy (aRR 0.65, 95% CI 0.44-0.98). *P. aeruginosa*identification was not associated with ongoing use of respiratory support or mortality at 3 years post-tracheostomy on adjusted analysis. Any pathogen identification was not associated with any of the measured 3-year outcomes.

In further examination of covariates, increasing number of CCCs per child was found to be significantly associated with the primary outcome of ongoing use of respiratory support at 3 years post-tracheostomy for all models regardless of the predictor group (**Appendix Table**). Non-White, non-Black race (classified as "Other" race) was identified to be a significant covariate in the association of culture predictors with mortality by 3 years.

Survival and time-to-event analyses

Survival analysis confirmed a lower cumulative survival probability for children with chronic *P. aeruginosa* identification as compared to children without chronic *P. aeruginosa* (**Figure 2c** , p=0.04). No significant differences in survival probability were identified between children with any pathogen identification vs. none and between children with any *P. aeruginosa* identification vs. none (**Figure 2a-b**).

Discussion

In this single-center retrospective cohort study of infants and young children with BPD and tracheostomies, identification of pathogenic respiratory bacteria including *P. aeruginosa* on respiratory culture was not associated with continued need for any respiratory support (e.g., oxygen, positive pressure) at 3 years post-tracheostomy placement. However, *P. aeruginosa* identification was associated with decreased probability

of decannulation by 3 years. Furthermore, the small subpopulation of children with chronic *P. aeruginosa* had a distinctly lower survival probability as compared with children with no bacterial isolation or only sporadic *P. aeruginosa* isolation, an association that was not explained by differences in medical complexity. Our findings suggest that respiratory tract *P. aeruginosa* , when identified sporadically, may not influence long-term respiratory dysfunction, but does delay decannulation. Findings also raise the question of whether chronic *P. aeruginosa* is inherently harmful or if it is representative of other important sequelae driving mortality.

The lack of association between presence of respiratory bacteria, including *P. aeruginosa* , and continued use of respiratory support at 36 months post-tracheostomy placement suggests that identification of pathogenic bacteria, whether during ARI or during surveillance testing, may not directly cause or propagate respiratory dysfunction. This is in contrast to what is known among other populations (i.e., cystic fibrosis, COPD), in which such pathogenic respiratory bacteria has been demonstrated to decrease lung function over time, as directly measured by pulmonary function testing and indirectly measured by disease exacerbation risk.[14-18,25-30] This lack of association with ongoing respiratory support among children with tracheostomies is particularly important because it was identified in spite of the fact that children with pathogen identification had far more cultures obtained than their peers without pathogen identification. In additional analysis of what factors do drive untimely respiratory support weaning, not surprisingly, a child's number of complex chronic conditions was associated with continued need for respiratory support in this cohort. While this finding has been described elsewhere,[31] the interaction between complexity and pathogenic organism identification warrants further study, as does the role of bacterial quantity and timing in relation to outcomes.

In contrast, children with any identification of *P. aeruginosa*had only half the probability of achieving decannulation by 3 years post-tracheostomy, suggesting delayed time to decannulation. This effect was additive, with each instance of *P. aeruginosa* identification decreasing the associated decannulation probability by 35%. This important association was not observed for the collective predictor of any respiratory pathogen identification, but instead was specific to*P. aeruginosa* .

In the setting of *P. aeruginosa* isolation specifically, we hypothesize that children with *P. aeruginosa* identification may be more prone to chronic respiratory symptoms, and therefore be poor candidates for decannulation. This group may also have more frequent culture testing obtained, which, if cultures are positive and are being treated with antimicrobials, could lead to delays. It is also possible that children with other respiratory causes for delayed time to decannulation, such as comorbid airway malacia, obstructive sleep apnea, subglottic stenosis, or other anatomical considerations are more likely to have *P. aeruginosa* identified on respiratory cultures. There is some limited evidence of an association between malacia and stenosis with non-pseudomonal respiratory bacteria in other pediatric populations, but it is not clear if *P. aeruginosa* exerts a direct or indirect influence on airway anatomy, or if this effect would be enough to delay decannulation or lead to a requirement for surgical airway reconstruction.[32-34]

Furthermore, clinicians may perceive an elevated risk of future respiratory illness due to *P. aeruginosa* and thus hesitate to swiftly decannulate following liberation from respiratory support. Our prior analysis from this cohort identified that *P. aeruginosa*isolation is not associated with episodes of clinician-diagnosed ARI when controlling for repeated testing and colonization;[21] thus the decreased probability of achieving decannulation with *P. aeruginosa* is not likely explained by direct delays from culture-positive pseudomonal ARI diagnoses or treatments. However, the risk of future ARIs after prior*P. aeruginosa* is unknown. Similarly, clinicians might perceive a risk of respiratory dysfunction related to this organism (as is well-documented in cystic fibrosis, but not supported by our data here) and therefore proceed with caution towards decannulation.

In addition to potential respiratory-related reasons for delayed decannulation, active non-respiratory comorbidities could increase a child's risk for *P. aeruginosa* , as has been demonstrated in adults with chronic disease,[35-37] and may simultaneously de-prioritize or delay decannulation proceedings. Although we controlled for comorbid conditions broadly in the form of number of CCC categories in analysis, specific relevant comorbidities may be unaccounted for. There may also be important social, family, or healthcare factors

influencing time to decannulation that do not affect time to wean respiratory support. At our institution, steps to wean respiratory support can be advanced in the outpatient or telemedicine settings. However, some steps for decannulation readiness evaluations necessitate hospital-based care (e.g., sleep studies, airway evaluations), which is more difficult and time-intensive to coordinate and requires children be illness-free for longer periods.

Although the prevalence of chronic *P. aeruginosa* identification in our cohort was very low – lower than reported elsewhere[19,20] – the 50% mortality rate identified in this group over the 3 years post-tracheostomy placement warrants attention. Whether this high mortality is a direct effect of *P. aeruginosa* itself or an indirect effect is unclear from our data, which lacks causes of death. Respiratory infections and antibiotic use are both associated with respiratory and gastrointestinal dysbiosis, which in turn each cause diminished immune system functioning and increased risk for further acute infection of various types, including ARI, among both murine models and humans.[38-41] It is furthermore possible that this group of children died of pseudomonal ARIs occurring after pseudomonal colonization; increased frequency of purulent tracheobronchitis and pneumonia have been documented among adults with tracheostomies who have tracheobronchial Gram-negative organism colonization.[42] On the other hand, children who are at risk for chronic *P. aeruginosa* due to immunocompromised status, comorbidities, or high hospital utilization are also likely at higher risk for mortality related to these non-pseudomonal factors, as has been reported in other populations.[37,43-47]

This study demonstrated a similar overall mortality rate to that reported in other studies of infants and young children with severe BPD and tracheostomies.[9] In survival analysis, we identified that most deaths occurred in the first 1 year following tracheostomy placement. In our adjusted analyses, children of non-White, non-Black race had a nearly threefold higher risk of 3-year mortality across predictor groups as compared with white peers; notably, the other covariates of sex, insurance type, and CCCs included in this model did not reach statistical significance. This racial disparity in such an important outcome raises concern for inequitable access to care, barriers to care utilization, inadequate cultural sensitivity or accommodations, or other socioracial factors that could underly this difference. This disparity follows some of the known racial differences in premature birth, a key risk factor for development of BPD.[48,49] More distally, Lewis et al. recently identified a 2-fold increased risk of the shorter-term outcome of NICU mortality among non-White infants with severe BPD in a multicenter study;[23] there was no racial difference in probability of tracheostomy placements in that study. Our findings provide some evidence that these racial mortality differences, likely the result of racist or biased institutional practices, persist beyond the NICU time course, but further study into causes and implications of longer-term outcome differences along racial lines is warranted.

This study has several limitations. Our study did not differentiate between bacteria identified during acute respiratory illness from bacteria identified in surveillance culture testing (i.e., during wellness). Although at our institution, children with tracheostomies are unlikely to seek medical care outside of CCHMC, it is possible that our study excluded respiratory cultures obtained from external sites, leading to potential rare misclassification of predictor status. The mortality rate of our population was higher than expected; our primary outcome was defined only for alive children, leading to possible selection bias for this analysis. The retrospective design of this study also creates potential for residual confounding, in which other clinical or demographic factors influencing respiratory pathogen detection and outcomes are not captured by our dataset. Furthermore, our center's results may not be generalizable to other institutions; our institution's positive culture prevalence is notably lower than that observed at other institutions,[20,50] but consistent with our prior internal studies.[21,44] This lower prevalence is hypothesized to be related to differences in our population and/or local factors (e.g., infection control policies, lab reporting procedures). Similarly, as noted above, the number of children meeting chronic *P. aeruginosa* identification criteria was very small which limits the conclusions from that subgroup's analyses.

Conclusion

Among children with BPD and tracheostomies, *P. aeruginosa* in the respiratory tract was associated with failure to decannulate by 3 years post-tracheostomy, but neither this organism nor pathogenic organisms collectively were found to be associated with evident respiratory dysfunction. Our findings suggest a unique,

less detrimental role of*P. aeruginosa* in the respiratory tract may exist for children with tracheostomies compared with that in other populations. This implies that active respiratory culture monitoring may be of limited benefit in promoting respiratory health in children with tracheostomies, though further investigation is necessary to confirm these relationships.

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Table 1. Patient cohort clinical characteristics.

	Full cohort (n = 170)	**Full cohort (n = 170)**	**Children with 1+ pathogen isolation (n = 101)**	**Children with 1+ pathogen isolation (n = 101)**	**Children without pathogen isolation (n = 69)**	**Children without pathogen isolation (n = 69)**	**p-value[a]**
Demographics	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	
Age at tracheostomy placement in months (median, [IQR])	4.1	[3.2, 5.3]	4.4	[3.5, 5.2]	3.9	[3.1, 5.6]	0.27
Male sex	93	(54.7%)	53	(52.5%)	40	(58.0%)	0.48
Primary insurance type Public Private Uninsured	97 62 11	(57.1%) (36.5%) (6.5%)	48 46 7	(47.5%) (45.5%) (6.9%)	49 16 4	(71.0%) (23.2%) (5.8%)	0.007
Race White Black Other[b]	96 45 29	(56.5%) (26.5%) (17.1%)	62 25 14	(61.4%) (24.8%) (13.9%)	34 20 15	(49.3%) (29.0%) (21.7%)	0.24
Hispanic ethnicity	2	(1.2%)	0	(0%)	2	(2.9%)	0.16
Clinical Characteristics							
Number of complex chronic condition categories[c] Median, [IQR] By category 1-3 4-5 6-7 8-9 10+	5 39 77 39 12 3	[4, 6] (22.9%) (45.3%) (22.9%) (7.1%) (1.8%)	5 18 49 20 11 3	[4, 6] (17.8%) (48.5%) (19.8%) (10.9%) (3.0%)	4 21 28 19 1 0	[3, 6] (30.4%) (40.6%) (27.5%) (1.5%) (0%)	0.04[e] 0.02
Home ventilator use[d]	115	(67.6%)	75	(74.3%)	40	(58.0%)	0.03

	Full cohort (n = 170)	**Full cohort (n = 170)**	**Children with 1+ pathogen isolation (n = 101)**	**Children with 1+ pathogen isolation (n = 101)**	**Children without pathogen isolation (n = 69)**	**Children without pathogen isolation (n = 69)**	**p-value[a]**
Number of cultures obtained per child (median, [IQR])	10	[3, 17]	12	[7, 18]	4	[2, 13]	<0.001

Abbreviations: IQR: interquartile range.

[a] p-value was determined using Chi-square or Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

[b] Category of "Other" race includes children with EMR race of more than 1 race category (10.0%), Asian (2.1%), American Indian and Alaska Native (1.3%), Pacific Islander (0.2%), Other (0.3%), and Refused or Unknown (3.1%).

[c] Represents each child's maximum number of complex chronic conditions over all encounters within the 3 year study period.

[d] Home ventilator use was defined at the time of first Pulmonary clinic visit after initial hospital discharge as the requirement, when well, for mechanical ventilation for any portion of the day or night and lasting for any duration of time after initial discharge with tracheostomy until 3 years after placement. Initial hospital discharge typically occurs several months after tracheostomy placement at our institution.

[e] p-value was determined using a generalized linear model.

Table 2. Respiratory culture characteristics.

	All cultures (n = 2,103)	**All cultures (n = 2,103)**	**Cultures with pathogenic organism[a] (n = 282, 13.4%)**	**Cultures with pathogenic organism[a] (n = 282, 13.4%)**	**Cultures without pathogenic organism (n = 1,821, 86.6%)**	**Cultures without pathogenic organism (n = 1,821, 86.6%)**	**p-value[b]**
Collection Details							
Specimen source Tracheostomy aspirate	1,394 709	(66.3 %) (33.7%)	246 36	(87.2%) (12.8%)	1,148 673	(63.0%) (37.0%)	<0.001
Bronchoalveolar lavage							
Child's age at culture collection	1.2	[0.7, 2.1]	0.7	[0.5, 1.3]	1.3	[0.7, 2.1]	<0.001

	All cultures (n = 2,103)	**All cultures (n = 2,103)**	**Cultures with pathogenic organism[a] (n = 282, 13.4%)**	**Cultures with pathogenic organism[a] (n = 282, 13.4%)**	**Cultures without pathogenic organism (n = 1,821, 86.6%)**	**Cultures without pathogenic organism (n = 1,821, 86.6%)**	**p-value[b]**
Diagnosis of acute respiratory infection[c] at culture collection[d]	630	(33.7%)	129	(45.7%)	501	(31.6%)	<0.001
Encounter type at culture collection Hospital admission Office visit Specimen collection only	1,864 145 94	(88.6%) (6.9%) (4.5%)	264 13 5	(93.6%) (4.6%) (1.8%)	1,600 132 89	(87.9%) (7.2%) (4.9%)	0.31
Department at culture collection Acute care Bronchoscopy Suite Critical care Emergency Department Pulmonology, Otolaryngology Clinic Other Clinic[e]	1,171 364 196 128 113 131	(55.7%) (17.3%) (9.3%) (6.1%) (5.4%) (6.3%)	191 8 58 6 13 6	(67.7%) (2.8%) (20.6%) (2.1%) (4.6%) (2.1%)	980 356 138 122 100 125	(53.8%) (19.5%) (7.6%) (6.7%) (5.5%) (6.9%)	<0.001
Culture Results							

	All cultures (n = 2,103)	**All cultures (n = 2,103)**	**Cultures with pathogenic organism[a] (n = 282, 13.4%)**	**Cultures with pathogenic organism[a] (n = 282, 13.4%)**	**Cultures without pathogenic organism (n = 1,821, 86.6%)**	**Cultures without pathogenic organism (n = 1,821, 86.6%)**	**p-value[b]**
Pathogenic organisms identified[a] Overall By species *Pseudomonas aeruginosa* *Staphylococcus aureus* *Klebsiella pneumoniae* *Serratia marscescens* *Moraxella catarrhalis* *Escherichia coli* *Klebsiella oxytocya* *Stenotrophomonas maltophilia* *Enterobacter* species Group A *Streptococcus* *Haemophilus influenzae* *Streptococcus pneumoniae*	282 107 98 39 30 20 13 11 9 9 8 6 2	(13.4%) (5.1%) (4.7%) (1.9%) (1.4%) (1.0%) (0.6%) (0.5%) (0.4%) (0.4%) (0.4%) (0.3%) (0.1%)	282 107 98 39 30 20 13 11 9 9 8 6 2	(100%) (37.9%) (34.8%) (13.8%) (10.6%) (7.1%) (4.6%) (3.9%) (3.2%) (3.2%) (2.8%) (2.1%) (0.7%)	– –	– –	– –
Polymicrobial growth	83	(3.9%)	83	(29.4%)	–	–	–
WBCs quantified on gram stain[f] Many Moderate Few Very few None	806 454 401 289 135	(38.3%) (21.6%) (19.1%) (13.7%) (6.4%)	144 62 44 20 10	(51.1%) (22.0%) (15.6%) (7.1%) (3.5%)	662 392 357 269 125	(36.4%) (21.5%) (19.6%) (14.8%) (6.9%)	<0.001

Abbreviations: IQR: interquartile range; WBCs: white blood cells.

[a] Pathogenic organisms were defined *a priori* as organisms that are not expected to be found in oropharyngeal flora, according to our Microbiology Lab's guidelines as previously described.[21]

[b] Calculated using generalized linear mixed models.

[c] Acute respiratory infection defined as presence of an International Classification of Diseases-Ninth or Tenth Revision diagnosis code (consistent with previously described codes[21]) during the encounter in which culture was collected.

[d] Excludes 234 cultures for which no diagnosis data was available.

[e] Primary care or other subspecialty clinic.

[f] Excludes 18 culture results without documentation of WBC count.

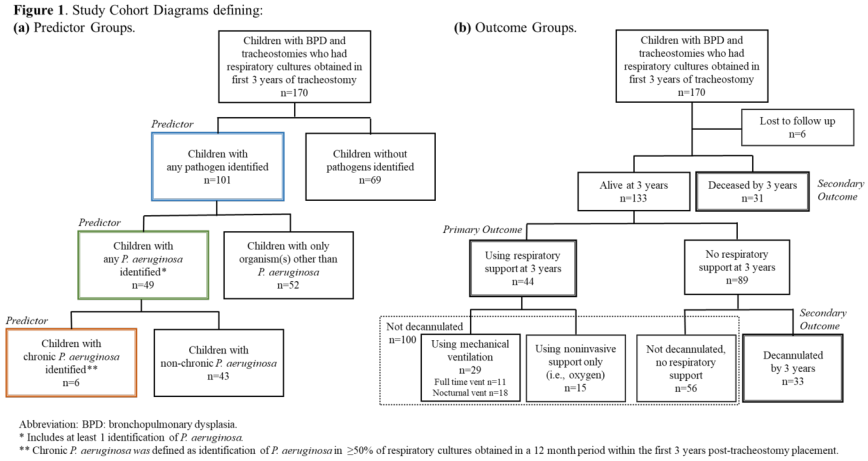


Table 3. Unadjusted analysis of outcomes.

Primary Outcome	Overall[a] (n = 133)	Overall[a] (n = 133)	Overall[a] (n = 133)	Using respiratory support at 36 months (n = 44)	Using respiratory support at 36 months (n = 44)	No respiratory support at 36 months (n = 89)	No respiratory support at 36 months (n = 89)	p-value
Primary predictor Any pathogen	83	83	(62.4%)	25	(56.8%)	58	(65.2%)	0.35

Primary Outcome	**Overall[a] (n = 133)**	**Overall[a] (n = 133)**	**Overall[a] (n = 133)**	**Using respiratory support at 36 months (n = 44)**	**Using respiratory support at 36 months (n = 44)**	**No respiratory support at 36 months (n = 89)**	**No respiratory support at 36 months (n = 89)**	**p-value**
Secondary predictors	41 3	(30.8%) (2.3%)	(30.8%) (2.3%)	11 1	(25.0%) (2.3%)	30 2	(33.7%) (2.3%)	0.31 0.99
Any *Pseudomonas aeruginosa*								
Chronic *Pseudomonas aeruginosa*[c]								
Secondary Outcome: Decannulation	**Overall[a] (n = 133)**	**Overall[a] (n = 133)**	**Overall[a] (n = 133)**	**Decannulated (n = 33)**	**Decannulated (n = 33)**	**Not decannulated (n = 100)**	**Not decannulated (n = 100)**	**p-value**
Primary predictor Any pathogen	83	(62.4%)	(62.4%)	21	(63.6%)	62	(62.0%)	0.87
Secondary predictors	41 3	(30.8%) (2.3%)	(30.8%) (2.3%)	6 0	(18.2%) (0%)	35 3	(35.0%) (3.0%)	0.07 0.57
Any *Pseudomonas aeruginosa*								
Chronic *Pseudomonas aeruginosa*[c]								
Secondary Outcome: Mortality	**Overall (n = 164)**	**Overall (n = 164)**	**Overall (n = 164)**	**Deceased (n = 31)**	**Deceased (n = 31)**	**Alive (n = 133)**	**Alive (n = 133)**	**p-value**
Primary predictor Any pathogen	98	(59.8%)	(59.8%)	15	(48.4%)	83	(62.4%)	0.15

Primary Outcome	**Overall[a] (n = 133)**	**Overall[a] (n = 133)**	**Overall[a] (n = 133)**	**Using respiratory support at 36 months (n = 44)**	**Using respiratory support at 36 months (n = 44)**	**No respiratory support at 36 months (n = 89)**	**No respiratory support at 36 months (n = 89)**	**p-valu**
Secondary predictors	49 6	(29.9%) (3.7%)	(29.9%) (3.7%)	8 3	(25.8%) (9.7%)	41 3	(30.8%) (2.3%)	0.58 0.08
Any *Pseudomonas aeruginosa*								
Chronic *Pseudomonas aeruginosa*[c]								

[a] Of children who were alive at 36 months.

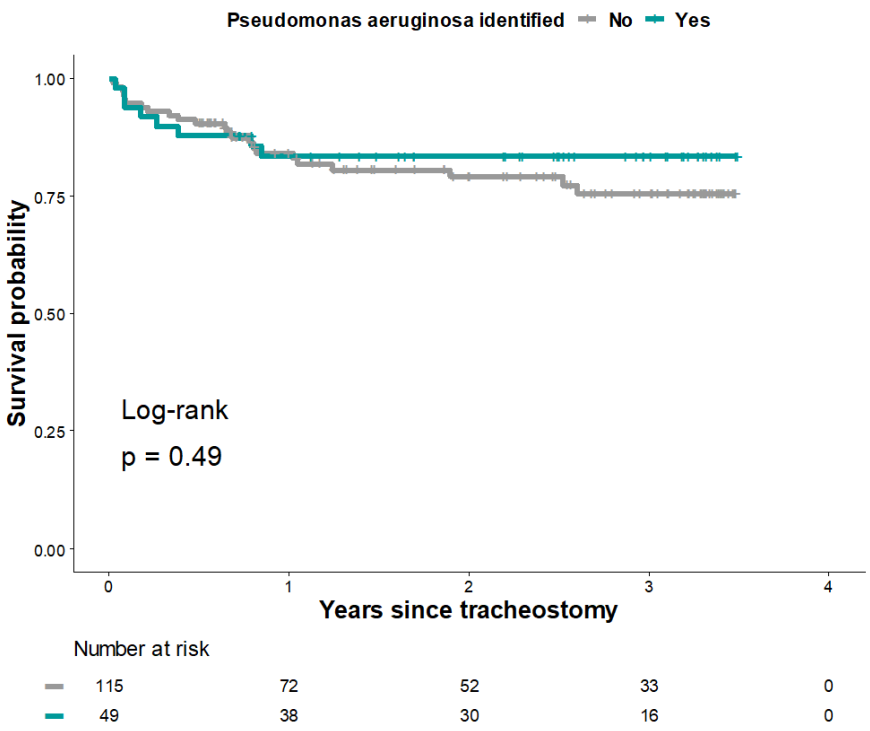
[b] p-value was determined using Wilcoxon rank sum testing for continuous variables and Chi-square test for categorical variables.

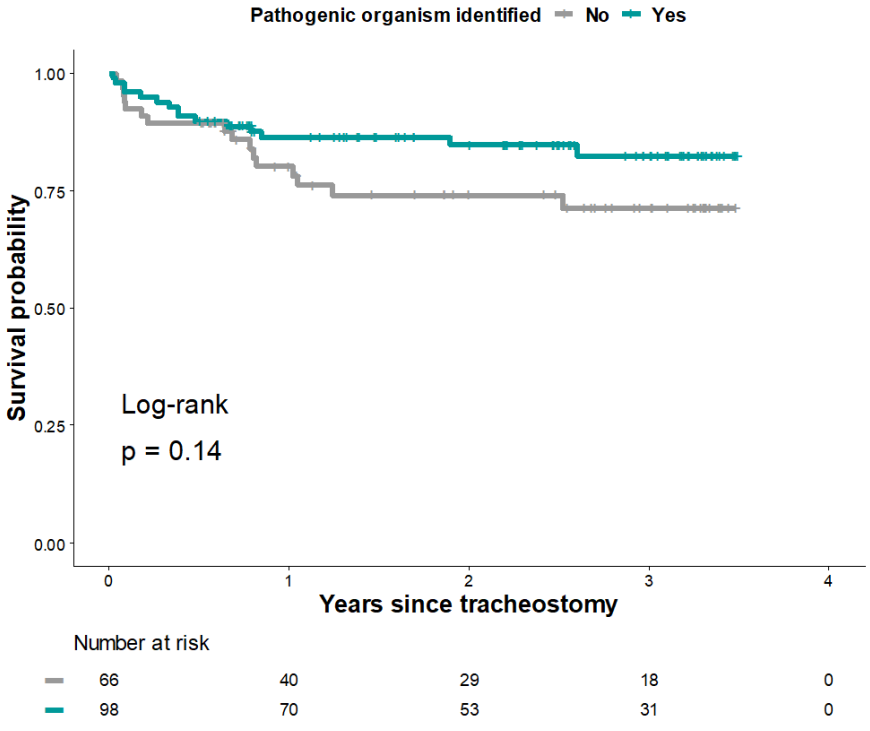
[c] Chronic *P. aeruginosa* defined as *P. aeruginosa* identification in [?]50% of respiratory cultures obtained in a 12 month period of the first 3 years post-tracheostomy placement.

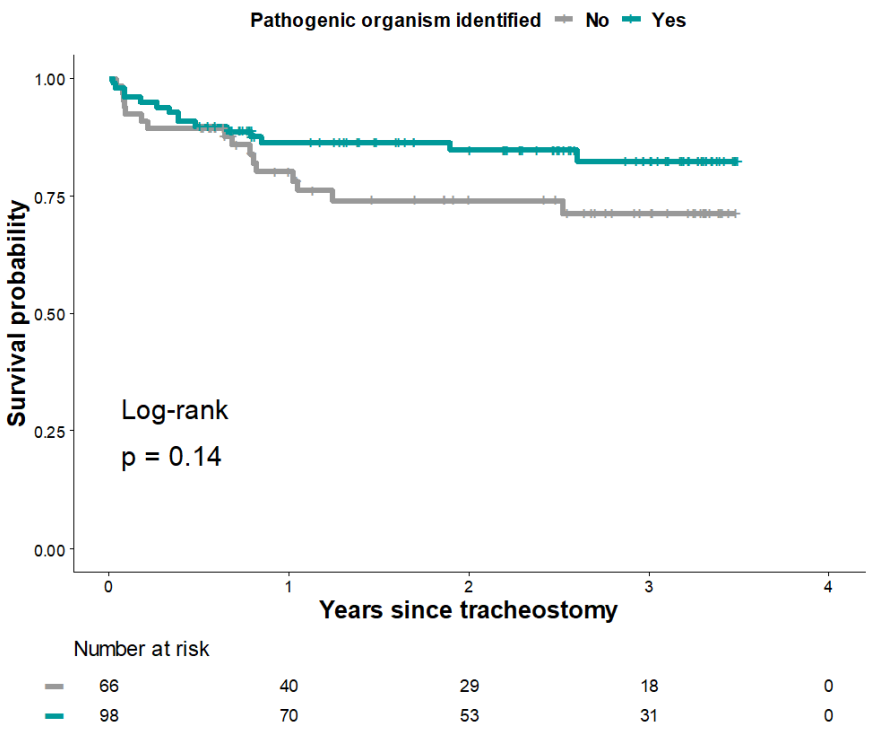
Figure 2. Adjusted analysis of outcomes.

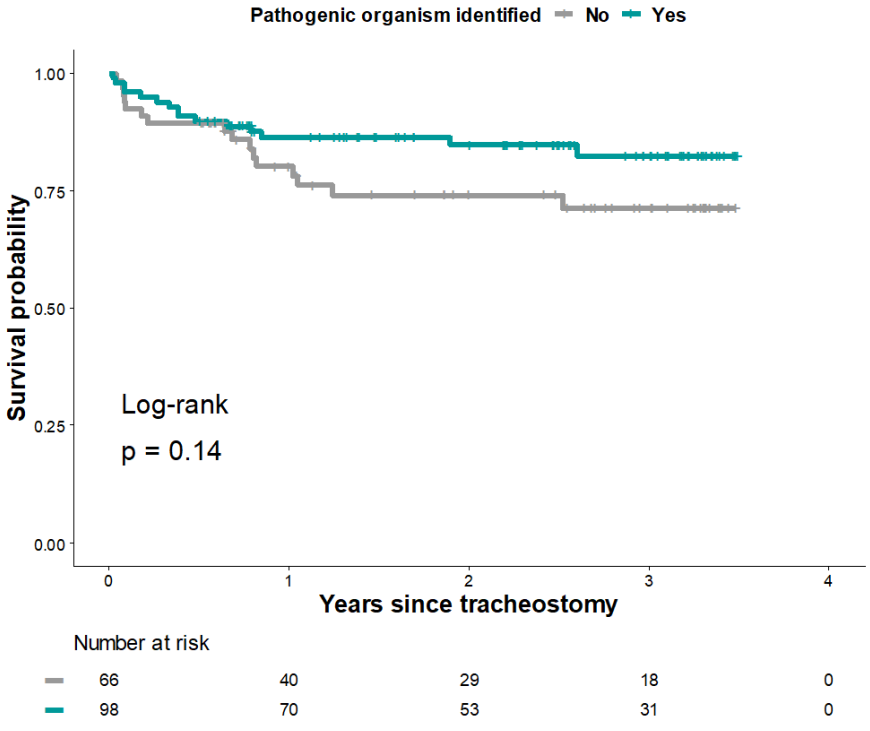
Analyzed using Poisson regression with robust standard errors controlling for child sex, race, insurance type, and number of complex chronic conditions.

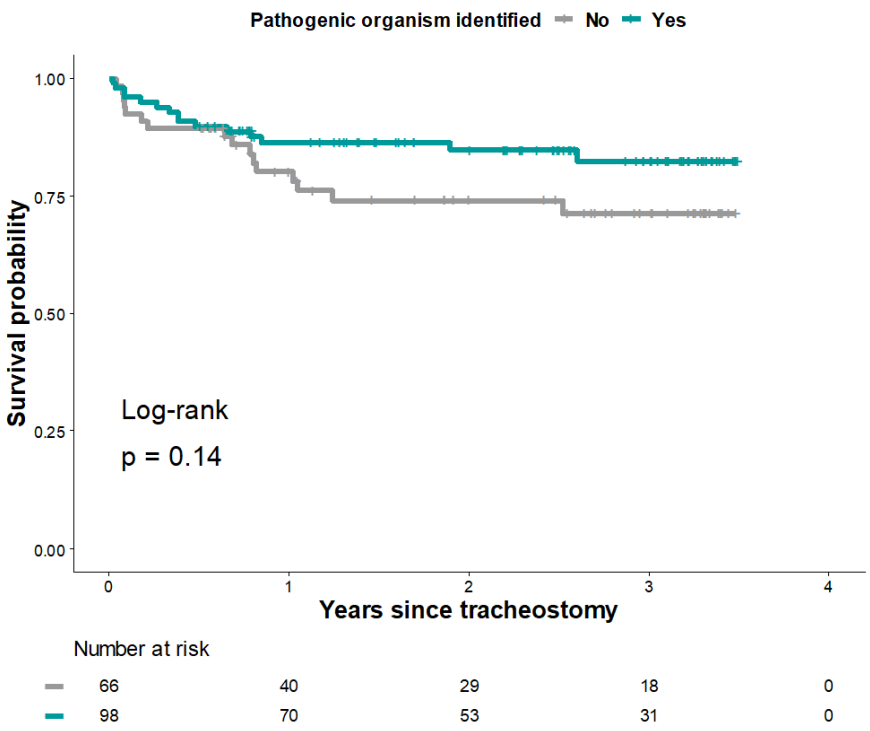
Figure 2. Survival Analysis.

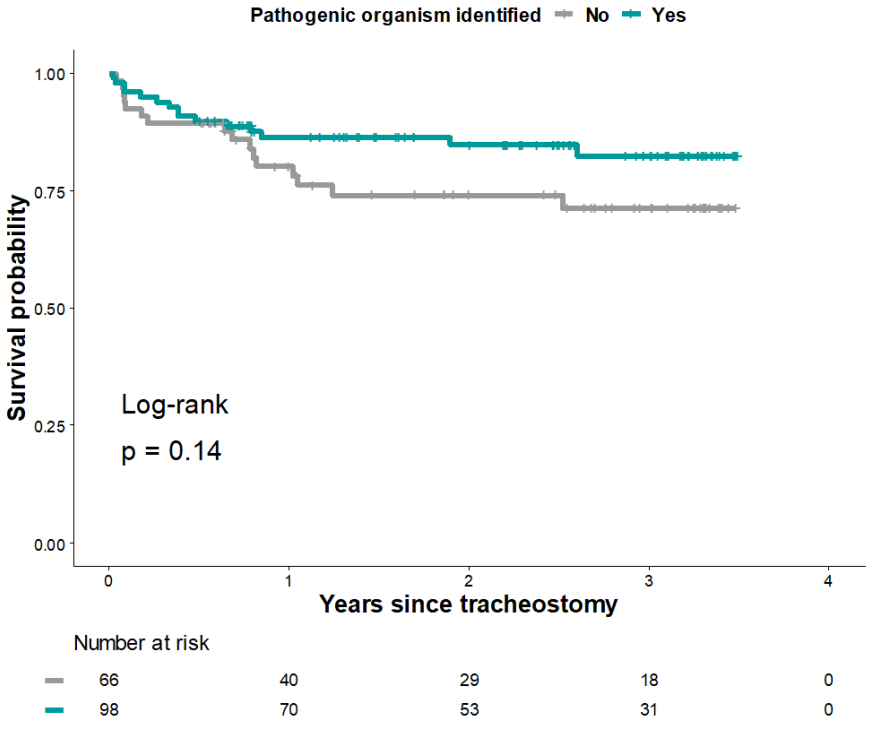


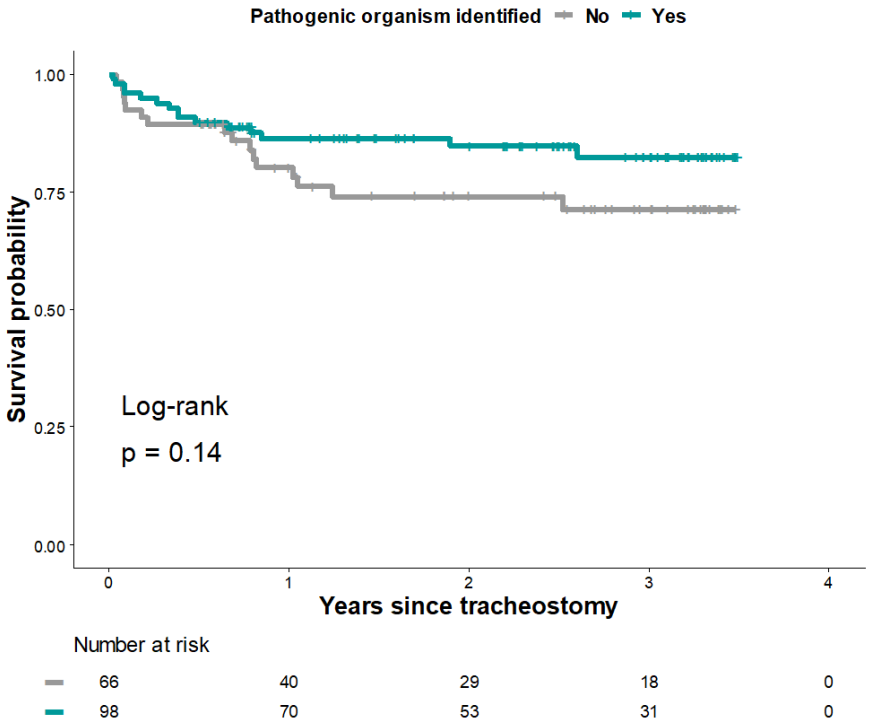












Plots of cumulative survival probability for 3-years post-tracheostomy for the following groups: a) children with any pathogenic organism identified vs. none, b) children with *Pseudomonas aeruginosa* identified vs. none, and c) children with chronic *Pseudomonas aeruginosa*identified vs. none.

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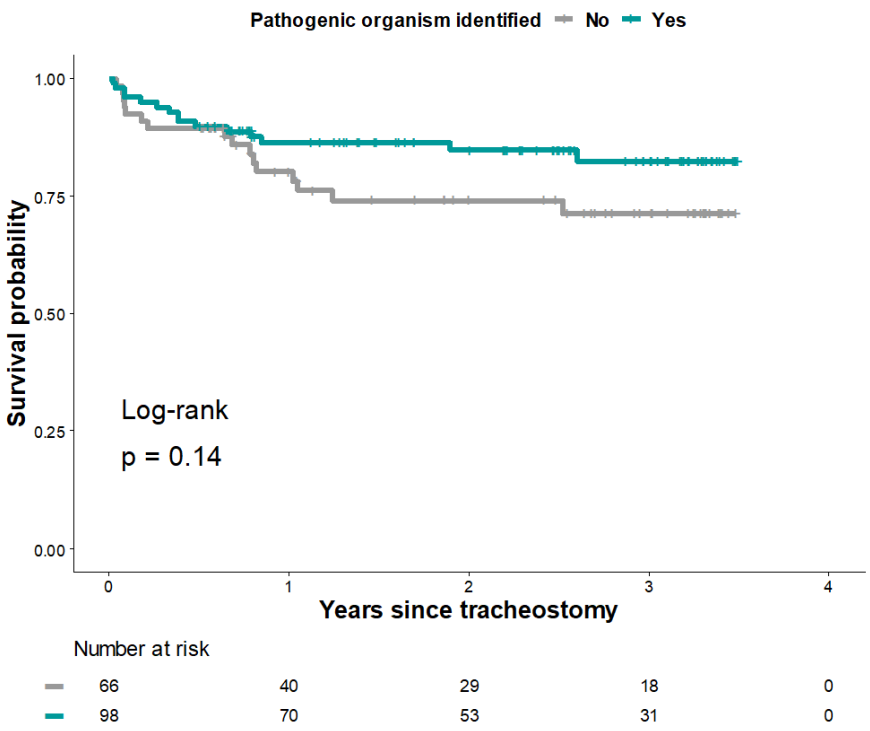

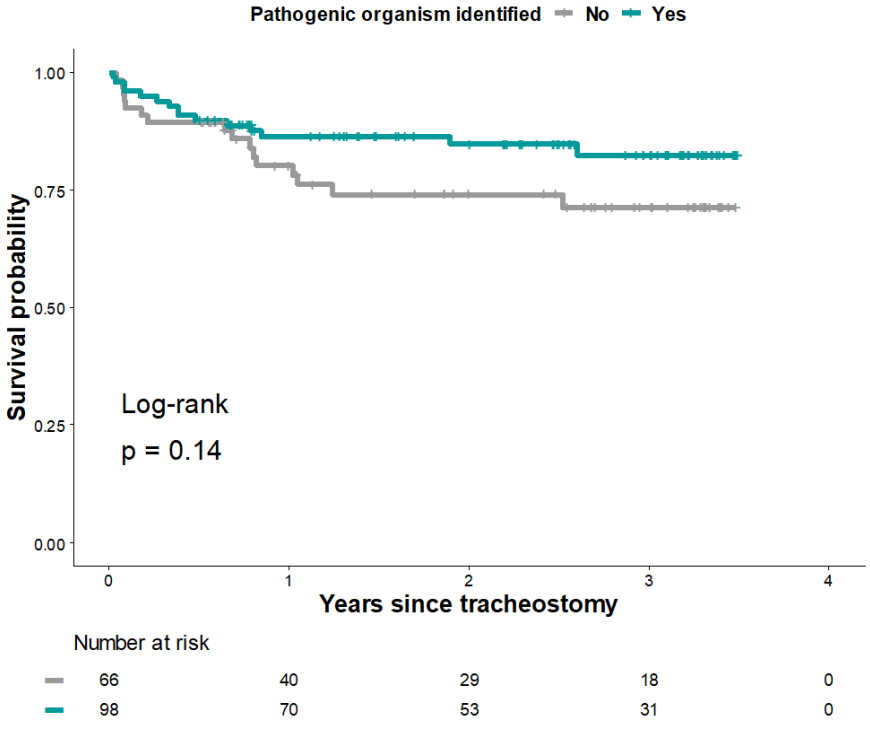

Appendix Table. Significant covariates from adjusted analyses of outcomes.

	Outcomes:	Ongoing respiratory support at 36 months:	Ongoing respiratory support at 36 months:	Decannulation by 36 months:	Decannulation by 36 months:	Death by 36 months:	Death by 36 months:	Death by 36 months:	Death by 36 months:
	Significant Covariates*:	*CCC count*	*CCC count*	*Female Sex (vs. Male)*	*Female Sex (vs. Male)*	*Black Race (vs. White)*	*Black Race (vs. White)*	*Other Race (vs. White)*	*Other Race (vs. White)*
		aRR (95% CI)	p-value	aRR (95% CI)	p-value	aRR (95% CI)	p-value	aRR (95% CI)	p-value
Predictors	Any pathogen	**1.20 (1.06-1.35)**	0.004	1.75 (0.95-3.23)	0.07	1.45 (0.59-3.55)	0.42	**2.78 (1.33-5.82)**	0.02
	Count of pathogens	**1.18 (1.04-1.35)**	0.01	1.74 (0.95-3.19)	0.07	1.45 (0.59-3.53)	0.41	**2.85 (1.38-5.89)**	0.005
	Any *P. aeruginosa*	**1.22 (1.07-1.38)**	0.002	**1.86 (1.02-3.37)**	0.04	1.50 (0.61-3.66)	0.38	**2.90 (1.41-5.98)**	0.01
	Count of *P. aeruginosa*	**1.20 (1.05-1.37)**	0.007	**1.88 (1.04-3.41)**	0.04	1.46 (0.58-3.68)	0.42	**2.89 (1.37-6.10)**	0.01

Abbreviations: aRR: adjusted risk ratio; CI: confidence interval; CCC: complex chronic conditions.

Analyzed with 12 predictor-outcome models using Poisson regression with robust standard errors, each model controlling for child sex, race, insurance type, and number of complex chronic conditions.

* Of the 4 covariates included in all models, only CCC count was significantly associated with the outcome of Ongoing respiratory support at 36 months; only sex was significantly associated with the outcome of Decannulation by 36 months; and only race was significantly associated with the outcome of Death by 36 months. All other covariates were not statistically significant in the respective models.