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**TITLE:** Hospital Outcomes for Pediatric Heart Transplant Recipients Undergoing Tracheostomy: A Multi-Institutional Analysis

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Dr. Spinner designed the study, collected the data, performed data analysis, drafted the initial article, and revised the final article. Drs. Cabrera and Denfield conceptualized the study and critically reviewed and revised the final article. Drs. Puri, Morris, and Wang assisted with data analysis and critically reviewed and revised the final article. Drs. Adachi, Costello, Dreyer, Heinle, Moffett, Price, Shekerdemian, and Tunuguntla critically reviewed and revised the final article.

ABSTRACT

Tracheostomy is associated with increased mortality and resource utilization in children with congenital heart disease (CHD). However, the prevalence and hospital outcomes of tracheostomy in children with heart transplant (HTx) are not known. We describe the prevalence and compare the post-HTx hospital outcomes of pediatric patients with pre-HTx tracheostomy (Pre-TT) and post-HTx tracheostomy (Post-TT) to those without tracheostomy. A multi-institutional retrospective cohort study was performed using the Pediatric Health Information System database. Hospital mortality, mediastinitis, length of stay (LOS), and costs were compared among patients with Pre-TT, Post-TT, and no tracheostomy. Pre-TT was identified in 29 (1.1%) and Post-TT was identified in 41 (1.6%) of 2,603 index HTx hospitalizations. Patients with Pre-TT were younger and more likely to have CHD, a non-cardiac birth defect, or an airway anomaly compared to those without Pre-TT. Pre-TT was not independently associated with increased post-HTx in-hospital mortality. Age at HTx < 1 year, CHD, and Post-TT were associated with increased in-hospital mortality. Pre-TT that occurred during the HTx hospitalization and Post-TT were associated with increased resource utilization. Tracheostomy was not associated with mediastinitis.
1. Introduction

The medical complexity of children who undergo pediatric heart transplantation (HTx) is increasing, and comorbidities including deconditioning, poor nutrition, muscular weakness, airway anomalies, and pulmonary dysfunction render a proportion of these children ventilator-dependent prior to undergoing HTx. Positive pressure ventilation improves cardiac output and reduces left ventricular afterload, myocardial oxygen demand, and respiratory muscle oxygen consumption. However, prolonged intubation in children decreases the patient’s comfort, limits mobility, and delays development of oropharyngeal skills. Furthermore, inadvertent extubation, vocal cord dysfunction, subglottic stenosis, and infection can lead to significant morbidity. Tracheostomy provides a stable airway and has many potential benefits including reduced risk of vocal cord dysfunction and subglottic stenosis, enhanced patient comfort, and improved pulmonary toilet to reduce risk of pulmonary infection. Tracheostomy allows for more rapid weaning of sedation with fewer days of vasoactive support and central venous access, and it can more easily facilitate physical rehabilitation and development of oromotor skills.

Post-operative tracheostomy can be carried out safely without major complications in children following surgery for congenital heart disease (CHD), but it is associated with increased in-hospital costs, length of stay (LOS), and mortality rates. However, the prevalence and post-HTx outcomes of children with pre-HTx tracheostomy (Pre-TT) and children with post-HTx tracheostomy (Post-TT) are not known. It is common for children awaiting HTx to be ventilator-dependent, and tracheostomy is increasingly being performed in children with cardiac disease. As the field of HTx evolves to address the challenges of the diverse group of children who reach end-stage heart failure, it is important to determine if Pre-TT and Post-TT are associated with worse overall post-HTx outcomes. The purpose of this study was to describe the prevalence of tracheostomy in children with HTx and to compare the in-hospital mortality rates and utilization of resources among children with Pre-TT, Post-TT, and HTx without tracheostomy.

2. Materials and Methods

2.1 Study Population and Design

We performed a multi-institutional, retrospective query of the Pediatric Health Information System (PHIS) database. The PHIS is an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation data from over 50 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children’s Hospital Association (Overland Park, KS), a business alliance of children’s hospitals. Data quality and reliability are assured through a joint arrangement with the Children’s Hospital Association and the American Academy of Pediatrics.

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effort between the Children’s Hospital Association and participating hospitals. For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, procedures, and costs. Data are de-identified at the time of data submission and are subjected to reliability and validity checks before being included in the database. The data that support the findings of this study are available from PHIS. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of PHIS.

Study Patients

We included all index hospitalizations of patients younger than 21 years of age who underwent HTx between January 2003 to December 2014. The International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9) procedure code 37.51 was used to define the HTx hospitalization and was the basis of inclusion into the study. Repeat HTx and multi-organ HTx were excluded. Data from subsequent hospitalizations were not included in the study.

2.2 Variables/Definitions

The primary exposure variable was tracheostomy present during the HTx hospitalization, which was subdivided into tracheostomy present pre-HTx and tracheostomy performed post-HTx. Procedure codes and dates of service were used to determine the timing of tracheostomy relative to HTx for each patient. The ICD-9 codes used to determine the presence and timing of tracheostomy are listed in the Supplement. As we sought to determine whether outcomes differed depending on the timing of tracheostomy placement, patients were defined as “Pre-TT” if tracheostomy occurred (and was still present) prior to HTx; all other patients (including those who underwent tracheostomy after HTx) were defined “Not Pre-TT”. Pre-TT was broken down into 2 groups: “prior hospitalization” Pre-TT if tracheostomy occurred at a hospitalization prior to the HTx hospitalization (and was still present) and “same hospitalization” Pre-TT if tracheostomy occurred during the HTx hospitalization prior to HTx. Not Pre-TT was also broken down into 2 groups: “Post-TT” if tracheostomy occurred after HTx and “NEVER” if no tracheostomy occurred. Patients were excluded from the analysis if the relative timing of tracheostomy could not be determined.

Covariates included demographics and a coexisting diagnosis of CHD, additional non-cardiac birth defect, and airway anomaly. The presence of CHD was determined using ICD-9 codes 745.x – 747.x. Birth defects were identified using ICD-9 codes 740.0 – 759.9. Airway anomalies were identified using ICD-9 codes 748.x. Outcome measures included in-hospital mortality, LOS, total costs, and mediastinitis.
Mediastinitis was identified using ICD-9 code 519.2. The wage and price index (published annually in the Federal Register) adjusted charges for each unit of service, and annual hospital- and department-specific ratio of cost-to-charge (RCC) were obtained from PHIS. Adjusted hospital costs were calculated by multiplying the adjusted charge by the relevant RCC then further inflated to 2015 US dollars using the medical care services component of the Consumer Price Index. Total costs and adjusted overall cost were calculated for each patient as the sum of the daily costs during the hospitalization.

2.3 Statistical Analysis

Descriptive statistics were reported using proportions for categorical variables and median and interquartile range (IQR) for continuous variables. Categorical and continuous variables were compared using chi-squared/Fisher exact and nonparametric tests as appropriate. Univariate and multivariable analyses were performed using generalized estimating equations for categorical outcomes and mixed modeling for continuous outcomes to account for clustering within hospitals. Factors with p-value < 0.3 on univariate analysis were considered for inclusion in the multivariable analysis models. Backward elimination was performed for multivariable analysis, retaining factors with p-value < 0.1. Two-tailed test of significance was used in all statistical analyses with statistical significance defined as p < 0.05. SPSS 22.0 (IBM, Armonk, NY) and SAS 9.4 (SAS Institute Inc., Cary, NC) were used for data analysis.

3. Results

Study Patients

There were 2,643 index HTx hospitalizations between January 2003 and December 2014. We excluded 40 patients who underwent repeat HTx. In the remaining 2,603 patients, a tracheostomy was identified in 74 patients, yielding an overall prevalence of 2.8%. We excluded 4 patients with an unknown timing of tracheostomy. Included in the final analysis were 29 patients with Pre-TT (1.1%) and 41 patients with Post-TT (1.6%). Post-TT occurred on median post-operative day 44 (IQR 26 - 69). Of the 29 patients with Pre-TT, there was 1 patient in which pre vs same hospitalization could not be determined (Figure 1).

We first compared the characteristics of patients who underwent tracheostomy placement prior to HTx (Pre-TT) compared to those who did not (Not Pre-TT). Compared to the Not Pre-TT group, patients with Pre-TT were younger and more likely to have CHD, an additional non-cardiac birth defect, and an airway anomaly (Table 1A). We then compared the characteristics of patients among NEVER and all tracheostomy groups and found differences in age and presence of CHD, additional non-cardiac birth defect, and airway anomaly (Table 1B). When compared to the NEVER group, patients with same
hospitalization Pre-TT were most likely to be younger than 1 year of age (p < 0.001), have CHD (p = 0.002), or have an additional non-cardiac birth defect (p < 0.001).

**Outcomes:**

The overall post-HTx in-hospital mortality rate for the entire cohort was 5.8% (n = 150). Younger age, presence of CHD, and race/ethnicity listed as “other” were associated with increased in-hospital mortality on univariate analysis (Table 2). We then assessed outcomes based on the timing of tracheostomy placement. The in-hospital mortality rate of patients with Pre-TT was 14% compared to 6% for the Not Pre-TT group (p=0.07). However, when the timing of Pre-TT was broken down, same hospitalization Pre-TT was associated with greater than four-fold increased odds of in-hospital mortality when compared to Not Pre-TT (OR 4.2, 95% CI 1.2 – 14.9). There was no difference in the odds of in-hospital mortality between prior hospitalization Pre-TT and Not Pre-TT (OR 1.4, 95% CI 0.2 – 10.7; Table 3A). For those with Post-TT, the odds of in-hospital mortality was four times greater compared to NEVER (OR 4.2, 95% CI 1.9 – 9.3; Table 3B). On multivariable analysis, age younger than 1 year, presence of CHD, and Post-TT were independently associated with increased adjusted odds of in-hospital mortality (Table 4). Pre-TT, irrespective of whether it occurred at a prior (OR 0.9, 95% CI 0.1 – 7.5) or same hospitalization (OR 1.8, 95% CI 0.05 – 6.9), was not independently associated with increased mortality.

The prevalence of mediastinitis was not different in patients with Pre-TT (n=1, 3%) compared to patients in the Not Pre-TT group (n=46, 2%; p = 0.97) or in patients with Post-TT (n=2, 5%) compared to patients in the NEVER group (n=44, 2%; p = 0.8). Patients with Pre-TT had longer hospital LOS (median 116 days vs 49 days; p < 0.001) and higher costs (median $839,780 vs $388,390; p < 0.001) compared to patients in the Not Pre-TT group. However, when the Pre-TT group is broken down, only patients with same hospitalization Pre-TT had longer LOS (Figure 2A) and higher costs (Figure 3A) when compared to patients in the Not Pre-TT group. Patients with prior hospitalization Pre-TT did not have different LOS (Figure 2A) or costs (Figure 3A) compared to patients in the Not Pre-TT group. Patients with Post-TT had increased LOS (Figure 2B) and higher costs (Figure 3B) compared to patients in the NEVER group. Of all patients that underwent a tracheostomy, 2 patients with Pre-TT (both were in the prior hospitalization group) and 5 patients with Post-TT were decannulated during the index transplant hospitalization.

4. Discussion

To our knowledge, this is the first multi-institutional report of the prevalence of Pre-TT and Post-TT rates among pediatric HTx patients, and the first comparison of the in-hospital mortality and resource
utilization of pediatric HTx patients with and without tracheostomy. While this study may have been underpowered to detect a significant difference between the in-hospital mortality of Pre-TT and Not Pre-TT, it reveals that HTx hospitalization outcomes are different between patients with prior hospitalization and patients with same hospitalization Pre-TT. Using an in-hospital mortality of 6% with an alpha of 0.05 and power of 80%, there would needed to have been 90 patients with pre-TT with an in-hospital mortality of 14% to be sufficiently powered. Despite the small number of overall tracheostomies in this cohort, patients with prior hospitalization Pre-TT clearly have decreased mortality, LOS, and costs compared to patients with same hospitalization Pre-TT. This likely reflects that these are two distinct patient populations, and the anticipated post-transplant hospitalization outcomes after tracheostomy differ. Specifically, we found that children with a history of tracheostomy prior to the heart transplant hospitalization do not have increased in-hospital mortality or resource utilization following HTx compared to children undergoing HTx without a tracheostomy.

This study was not specifically designed to determine if a mechanically ventilated child should undergo tracheostomy while awaiting HTx. Determining the optimal timing of tracheostomy in pediatric cardiac surgery remains unclear, and randomized controlled trials (RCTs) to answer this specific question are not a realistic possibility due to the small number of patients and numerous complex contributory factors. In the limited previous studies of tracheostomy in pediatric cardiac patients, there is some evidence, consistent with the adult literature, that patients with “earlier” tracheostomy have better outcomes than do patients with “later” tracheostomy. Ortman et al. described 4 children who underwent tracheostomy prior to surgery for CHD; all 4 were still alive at 6 years follow-up, whereas more than half of 46 patients who underwent post-operative tracheostomy were deceased at 4 years follow-up. Johnson et al. described that later placement of post-operative tracheostomy in patients with CHD was independently associated with increased odds of in-hospital mortality. In the adult literature, RCTs of tracheostomy after cardiac surgery have revealed that “early” tracheostomy is associated with decreased mortality rates, fewer unscheduled extubations, and more sedation-free days.

The decision, timing, and anticipated post-HTx hospitalization outcomes for performing a tracheostomy in a child awaiting HTx should be considered on a case-by-case basis and should be influenced by the indication for tracheostomy. It has been consistently shown that upper airway anomalies are associated with decreased rates of post-tracheostomy mortality, and this should be considered for patients that undergo tracheostomy due to an upper airway abnormality. Although the indications for tracheostomy could not be assessed in this cohort, airway anomalies were present in...
over 60% of patients with prior hospital Pre-TT and did not increase the risk of post-HTx in-hospital mortality. In contrast, age younger than 1 year at HTx and history of CHD were independently associated with increased odds of mortality in our cohort. These findings are consistent with data from a large multi-institutional database reported by Berry et al., which revealed that CHD and age younger than 1 year were significantly associated with increased odds of in-hospital mortality in all children with tracheostomy. For mechanically ventilated children less than 1 year of age with CHD and end-stage heart failure awaiting HTx, pre-HTx tracheostomy may help optimize cardiopulmonary status prior to HTx and facilitate physical and occupational therapies with faster weaning from sedation. The increased in-hospital mortality in same hospitalization Pre-TT is likely more reflective of overall disease status rather than the presence of tracheostomy, as indicated by the multivariable analysis. It is possible that a sooner discussion to proceed with tracheostomy could help render this specific patient population better candidates for HTx. Future investigation into this issue is warranted.

One of the theoretical concerns regarding tracheostomy in children undergoing cardiac surgery, although it has not been borne out in the few published series in the pediatric literature, is whether there is an increased risk of mediastinitis due to the anatomical proximity of surgical sites. Another concern is whether this risk may be further augmented in patients requiring immunosuppression. Due to the limitations of the data construct of the PHIS database, the exact timing of mediastinitis could not be determined. However, we found no difference in the prevalence of mediastinitis in any of the groups of patients that underwent tracheostomy when compared to patients that did not undergo tracheostomy, which is an important addition to the existing knowledge base.

The prevalence (1.6%) of Post-TT is similar to the prevalence of post-operative tracheostomy after surgery for various forms of CHD. We also found that children undergoing tracheostomy following HTx are at increased risk for mortality, consistent with previous reports of post-operative tracheostomy following surgery for CHD is associated with increased mortality. The in-hospital mortality rate for Post-TT (20%) was less than half the mortality rate following post-surgical tracheostomy in infants with hypoplastic left heart syndrome (44%), although, not surprisingly, it was considerably higher than the in-hospital mortality rate following post-surgical tracheostomy in patients with a ventricular septal defect (7%). For tracheostomy following pediatric cardiac surgery, higher surgical risk is independently associated with increased in-hospital mortality. There are, therefore, important patient factors to be considered when assessing the risk of post-tracheostomy mortality.

There are important limitations inherent to the observational, retrospective database design of this study. The PHIS is a large administrative database that depends on accurate and thorough ICD-9 coding.
by participating institutions. Patient identification and classification of diagnosis relied on accurate ICD-9 codes. The sensitivity and specificity associated with ICD-9 codes is unknown, and inaccurate or incomplete ICD-9 coding may affect outcome analyses. Our patient cohort was limited through 2014 to stay within the ICD-9 coding era and minimize any variation in coding trends, hence we may not capture recent changes in trends of tracheostomy practice. However, the current cohort spans over a decade of experience. We could not determine the primary indication for tracheostomy or cause of death, and we could not take into account from the database specific clinical data such as number of failed extubation attempts. Patients who underwent tracheostomy and were listed but died prior to HTx were not included. In addition, we were not able to determine if patients were discharged on positive pressure ventilation, and the number of patients that were decannulated may be underestimated if they were decannulated at a non-PHIS hospital or as an outpatient. The number of tracheostomies may also be underestimated if a tracheostomy occurred at a center not included in the PHIS and if a diagnosis code for tracheostomy was not used; only 4 patients were identified with a diagnosis code of tracheostomy without a procedure code, and they were therefore excluded from the analysis (Figure 1). While we were able to identify mediastinitis, we were not able to identify episodes of surgical site superficial skin/soft tissue infections due to the limitation of PHIS not being able to specify the location of such coded infections; we therefore may potentially underestimate surgical site complications of post-surgical tracheostomy in this population. We were also not able to determine intermediate and long-term outcomes after tracheostomy including out-of-hospital respiratory infections, quality of life, or mortality. Database linkage is, therefore, an important future direction that may help determine long-term outcomes of tracheostomy in patients undergoing HTx to improve the risk-stratification and care of children that undergo HTx. This study is also limited by the total number of tracheostomies in children that undergo HTx, which incurs the risk of type II error. However, the utilization of a large administrative database permitted the inclusion of the largest reported cohort of pediatric heart transplant patients with tracheostomy in the literature.

5. Conclusion:

In this large multi-institutional study, pre-HTx tracheostomy was present in 1.1% of children who underwent a first-time HTx, and it was not an independent risk factor for increased post-HTx in-hospital mortality or mediastinitis. Post-HTx tracheostomy was present in 1.6% of children who underwent a first-time HTx, and it was associated with increased post-HTx in-hospital mortality, LOS, and cost compared to those without tracheostomy. Pre-transplant tracheostomy is a reasonable and safe
strategy warranting consideration in children awaiting heart transplant and requiring chronic ventilation.

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Disclosure: None

Figure Legends:

Figure 1: Distribution of Tracheostomies. Patients were defined as “Pre-TT” if tracheostomy occurred before heart transplant (HTx); all other patients were defined “Not Pre-TT”. Pre-TT was broken down into “Prior” if tracheostomy occurred at a hospitalization prior to the HTx hospitalization and “Same” if tracheostomy occurred during the HTx hospitalization prior to HTx. Not Pre-TT was broken down into “Post-TT” if tracheostomy occurred after HTx or “NEVER” if no tracheostomy occurred. There were 40 patients with repeat HTx that were excluded. There were 4 patients excluded due to an unknown timing of tracheostomy. One patient had a Pre-TT, but prior vs same hospitalization could not be determined.

Figure 2: Hospital Length of Stay.

2A: Pre-Transplant Tracheostomy vs Not. Patients with same hospitalization pre-transplant tracheostomy (Pre-TT) had longer length of stay (LOS) compared to patients in the Not Pre-TT group. Patients with prior hospitalization Pre-TT did not.

2B: Tracheostomy Status. Patients with same hospitalization Pre-TT and patients with post-transplant tracheostomy (Post-TT) had longer LOS compared to patients in the NEVER group. Patients with prior hospitalization Pre-TT did not.

Figure 3: Hospital Costs.

3A: Pre-Transplant Tracheostomy vs Not. Patients with same hospitalization pre-transplant tracheostomy (Pre-TT) had higher costs compared to patients in the Not Pre-TT group. Patients with prior hospitalization Pre-TT did not.

3B: Tracheostomy Status. Patients with same hospitalization Pre-TT
and patients with Post-TT had higher costs compared to patients in the NEVER group. Patients with prior hospitalization Pre-TT did not.

References


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Figure 1: Distribution of Tracheostomies

HTx: Heart Transplant; Pre-TT: Pre-transplant tracheostomy; Post-TT: Post-transplant tracheostomy

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Figure 2A – Length of Stay: Pre-Transplant Tracheostomy vs Not

Timing of Tracheostomy

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Figure 2B – Length of Stay: Tracheostomy Status

Timing of Tracheostomy

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<thead>
<tr>
<th>Treatment</th>
<th>Median (IQR)</th>
<th>p-value</th>
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<tr>
<td>Prior Hospital</td>
<td>140 (100-160)</td>
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<tr>
<td>Same Hospital</td>
<td>160 (130-180)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-TT</td>
<td>132 (120-140)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* denotes comparison to NEVER group.
Figure 3B - Hospital Costs: Tracheostomy Status

* denotes comparison to Never group

NEVER

Prior Hospital Pre-TT

Same Hospital Pre-TT

Post-TT

Cost ($)

$384,988

$429,203

$966,106

$1,023,166

*p = 0.2

*p < 0.01

*p < 0.001

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