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Anastomotic Leak and its Implications: A Multicenter Analysis of "Type C" Esophageal Atresia / Tracheo-esophageal fistula (EA/TEF)*



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A R T I C L E I N F O

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ABSTRACT

Purpose: Repair of type C esophageal atresia with tracheo-esophageal fistula (EA/TEF) may be complicated by esophageal anastomotic leak. Risk factors associated with leak and the impact of leak on inpatient outcomes remains uncertain. Our objectives are to estimate the associations between clinical factors and esophageal anastomotic leak and quantify the association of leak with length of stay (LOS) in infants who underwent repair of type C EA/TEF.

Methods: Using the Children's Hospitals Neonatal Database (CHND), we identified infants with type C EA/TEF from 2021 to 2023. The main outcomes were anastomotic leak and LOS. Multivariable associations between patient and clinical factors and these outcomes were quantified using logistic regression (leak) and Cox proportional hazards modelling (LOS).

Results: Among 365 infants at 36 centers, anastomotic leak occurred in 55 (15.1 %) infants, and thoracoscopic approach, lower birthweight, small for gestational age less than 10th percentile, male sex, staged repair, ventricular septal defect, and center were independently associated with leak (area under receiver operating curve = 0.853). Also, LOS was increased in infants with leak compared to those without [hazard ratio (HR): 0.655, 95 % CI = 0.431–0.996, p = 0.044], independent of birth weight, surgical approach, male sex, or VSD. The adjusted LOS demonstrated a 11-fold inter-center variation (p = 0.034).

Conclusions: Several clinical and operative factors are associated with esophageal anastomotic leak in infants after type C EA/TEF repair. Leak significantly prolongs LOS. The magnitude of inter-center variability in LOS also suggests that identifying best practices could aid in improving patient care in this patient population.

Type of study: Retrospective Comparative Study.

Level of Evidence: III.

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Abbreviations: CHNC, Children's Hospitals Neonatal Consortium; EA/TEF, Esophageal Atresia/Tracheo-esophageal Fistula; LOS, Length of Stay; NICU, Neonatal Intensive Care Unit.

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1. Introduction

Esophageal atresia with tracheoesophageal fistula (EA/TEF) is one of the most common congenital anomalies of the esophagus, occurring at a rate of 1 in every 4000 live births [1]. EA/TEF is classified by the presence and location of the tracheoesophageal fistula (TEF). The most common configuration, type "C," involves proximal esophageal atresia with a fistula between the trachea and distal esophagus and makes up about 85 % of EA/TEF cases [2]. EA/ TEF patients require extensive longitudinal multidisciplinary care which is likely to minimize the incidence and effect of known complications, such as anastomotic leak, prolonged hospital length of stay, and esophageal stricture.

Esophageal anastomotic leak may be diagnosed by esophagram after the repair or may become clinically apparent when there is saliva draining from a chest tube, new development of an air leak or pneumothorax, or clinical signs of sepsis and mediastinitis. Anastomotic leaks can be related to subsequent delays in oral feeds and may require antibiotic therapy, drain placement, or rarely, reoperation. Leaks may also be associated with greater risk of esophageal anastomotic stricture [3,4].

Although the minimally invasive approach is becoming more common for repair of EA/TEF, there are few large multi-institutional studies examining associations between thoracoscopy versus open surgery and the incidence of leak [5]. Studies evaluating the use of transanastomotic feeding tube (TAFT) and post-operative leak have not shown an association, although an increase in stricture was noted with TAFT placement [6,7]. With regard to length of stay (LOS), it is possible that excess LOS for EA/TEF patients is driven more by prematurity and other comorbid conditions as opposed to the presence of anastomotic leak, but this has not been wellstudied. Predicting the likelihood of leak and understanding which patient- and operation-related factors are associated with an increased risk of leak, in addition to excess LOS, may influence perioperative decision-making and inform how parents are counseled regarding expected outcomes.

Our study aimed to estimate the associations of clinical and demographic factors with the occurrence of esophageal anastomotic leak in infants undergoing type C EA/TEF repair. We also aimed to quantify the impact of anastomotic leak on LOS. We hypothesized that comorbidities and operative factors would be related to the likelihood of leak and LOS.

2. Methods

Accessing the registry on 2/1/2023, we conducted a retrospective cohort study on infants captured in the Children's Hospitals Neonatal Database (CHND). The CHND has captured inpatient clinical data from infants admitted to level IV, neonatal intensive care units (NICUs) in the US since 2010; however, we only analyzed data since April of 2021 when CHND began collecting diseasespecific parameters for neonates undergoing EA/TEF repair. We identified infants with type C EA/TEF in CHND during their first admission to a participating NICU. Infants who did not undergo an esophageal anastomosis and those with a length of hospitalization <3 days were omitted from the analysis.

The primary outcome was the presence of an esophageal anastomotic leak. This was defined in the CHND by the presence of a clinical leak (e.g., saliva in the chest tube) or leak demonstrated by an esophageal contrast study (esophagram). Trained data coordinators abstracted these data manually from review of the medical records for each infant using standardized variable definitions. The second main outcome was hospital LOS. Other clinical characteristics included mortality, central line days, age at parenteral nutrition (PN) discontinuation, need for esophageal dilation prior to discharge, proportion of patients with leak who required reoperation, and death.

Demographic and clinical factors were abstracted from the CHND and compared in infants with and without an anastomotic leak in univariable analyses. Selected variables included: gestational age, birthweight, small for gestational age ((SGA) < 10th percentile) [8], one- and 5-min Apgar scores, age at referral to CHNC center, sex, staged repair (when fistula repair and esophageal anastomosis were not performed at the same time), presence of ventricular septal defect (VSD), and VACTERL association, which was defined as those meeting at least 2 associated conditions in addition to EA/TEF [9]. Aortic arch position (left versus right) was also assessed. Operation-specific variables included extrapleural versus transpleural approach (extrapleural technique enters the posterior mediastinum without breaching the parietal pleura), and thoracoscopic versus thoracotomy approach. Cases that were converted to thoracotomy from thoracoscopy were analyzed in the thoracoscopic group. Since thoracoscopic approaches are transpleural, we performed a subgroup analysis of patients undergoing thoracotomy to evaluate the association between transpleural versus extrapleural approach and anastomotic leak. Additionally, we examined the association between intra-operative transanastomotic tube placement and anastomotic leak.

Chi square test was used to compare groups in terms of categorical variables, and Wilcoxon rank sum tests were completed for continuous variables. To determine the clinical, demographic, and patient factors associated with esophageal anastomotic leak, a multivariable logistic regression model was created with factors that were either hypothesized to be clinically relevant and statistically significant on univariable analysis (p < 0.2). In the multivariable model, we used birthweight but not gestational age at birth due to their anticipated collinearity. We did not include transpleural versus extrapleural approach in the multivariable model, since thoracoscopic repairs are performed transpleurally. We reported odds ratios and 95 % confidence intervals, as well as the adjusted receiver operating characteristic curves (ROC) with and without 'center' treated as a fixed effect. We further evaluated the model using the Hosmer–Lemeshow test.

The presence of an anastomotic leak was assessed as a risk factor for timing of inpatient discharge (*i.e.*, LOS) after surgical esophageal anastomosis. Patients that died were included initially and then omitted from the final models, as the differences in models were minimal (due to low rate of mortality). A Cox proportional hazards model was fitted to estimate the relationship between the presence of anastomotic leak and LOS. The observation period was 120 days post-operatively, based on clinical experience. Clinical, demographic, and/or surgical factors that were known prior to or at the time of the surgical anastomosis were considered in these regression equations. Proportional hazard assumptions were tested and not violated.

Additional clinical characteristics were compared using Chi–Square test, Fisher's exact and Wilcoxon Rank Sum Test as appropriate.

Statistical analyses were completed in SAS Enterprise Guide v8.3 (SAS Institute, Cary NC) and statistical significance set at p < 0.05. Institutional review board oversight was obtained by each participating center in CHND to enter clinical data into the registry; for secondary analyses, these analyses were considered exempt by the Stanley Manne Research Institute (Chicago, IL: #2011-14673).

3. Results

From CHND, we identified 629 babies with EA/TEF during the designated time frame, April 2021 to February 2023. After excluding those without type C EA/TEF (n = 127), those with a

length of hospitalization <3 days (n = 57), those with long-gap disease with their EA/TEF (n = 23), and those who did not undergo esophageal anastomosis (n = 57), 365 infants were included in this analysis (Supplementary Fig. 1). Of the 36 hospitals included in the study during the time period, the median case volume was 8 with an interquartile range of 5–13, and total range of 1–28.

Table 1 depicts infants with type C. EA/TEF stratified by the presence or absence of an esophageal anastomotic leak. There were 55 (15 %) infants who had a demonstrated clinical and/or radiographic leak. Infants with a leak were more likely to be male, have a lower birthweight, be born SGA <10th percentile, experience a thoracoscopic surgical approach, and have a VSD. In a subgroup analysis of patients who underwent open repair, those with a transpleural approach had a higher incidence of leak (15/93; 19.2%) vs those with extrapleural approach (15/170; 9.6 %, p = 0.004). In addition, operation time was longer for patients undergoing open transpleural versus open extrapleural repair (226 vs 196 min, p = 0.008). There were no significant associations between APGAR score at one or 5 min, age at referral to CHNC center, or age at EA/TEF repair and anastomotic leak. Table 1 lists the number in each category for each variable, and the number missing can be calculated by subtracting the sum of the observations in each category from the total N of 365. The percentage of observations with missing data was less than 5 % for all variables used in multivariable analysis.

In our cohort, patients who underwent thoracoscopic repair had a leak rate of 22 %, while those who underwent thoracotomy had a leak rate of 12 % (p = 0.031). Those with a staged repair had a greater frequency of leak than those whose fistula and esophageal anastomosis were completed concurrently (38 % vs 14 %, p = 0.004). Patients with intra-operative transanastomotic tube placement had similar proportions of leak compared to those without (12 % vs 14 %, p = 0.786).

On multivariable analysis, multiple factors including thoracoscopic approach, male sex, staged repair, and presence of VSD were

Table 2		
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Multivariable analysi	is of anastomotic leak.
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Variable	aOR (95 % CI)	Р
Median birthweight, 100 g	1 (1,1)	0.835
SGA (<10th percentile)	2.5 (1,6)	0.045
Male sex	2.5 (1.1,5.7)	0.028
Staged repair	12.5 (2.4,63.9)	0.002
Thoracoscopic approach	3.6 (1.3,9.6)	0.011
VSD	3.8 (1.6,9)	0.003
Center ($n = 23$)	Range: 0.3-8.3	<0.001

SGA: small for gestational age (Olsen 2010); VSD: ventricular septal defect; aOR = adjusted odds ratio; CI = confidence interval.

independently associated with the presence of an anastomotic leak (Table 2). This equation was associated with an area under the ROC curve of 0.719 (goodness of fit, chi-square p = 0.76) prior to the inclusion of 'center' which increased to 0.853 after inclusion (Fig. 1, goodness of fit, chi-square p = 0.21).

The second main outcome was LOS. The presence of an anastomotic leak was associated with increased LOS in unadjusted analysis (Fig. 2). Patients with anastomotic leak had a longer median length of hospital stay (50 days [IQR 31–91] vs 32 days [IQR 19–55], p = 0.016). This association persisted in multivariable analyses: anastomotic leak was associated with an increased time to discharge after adjusting for multiple factors (Table 3, adjusted hazard ratio (aHR) = 0.662 [95 % confidence interval (CI): 0.44, 1.0, p = 0.049). The range of center-level estimates range from 0.11 to 1.17 demonstrating an 11-fold (p = 0.034) difference in likelihood of discharge timing across the included centers (Fig. 3), with four centers demonstrating a significantly increased LOS relative to the median center. Individual center differences were difficult to estimate due to small sample sizes at some centers.

Additionally, we found leak to be associated with increased duration of central line days (median 24 [IQR 19-41] vs 15 [IQR

 Table 1

 Unadjusted association of anastomotic leak with demographic and clinical characteristics.

	Total (<i>N</i> = 365)	No leak <i>N</i> = 310 (84.9 %)	Leak N = 55 (15.1 %)	OR	P-value
Birthweight median [IQR]; g	2580 [2010,3090]	2666 [2040,3100]	2460 [1540,2958]	1 (0.9,1)	0.027
Gestational age median [IQR]; weeks	37 [35,39]	37 [35,39]	37 [34,39]	1 (0.9,1)	0.43
SGA <10th%tile					
Yes N (%)	74	53 (17.1)	21 (38.2)	3 (1.61,5.56)	0.001
No N (%)	291	257 (88.3)	34 (11.6)	Referent	
Sex					
Male N (%)	214	176 (82.2)	38 (17.8)	1.7 (0.92,3.15)	0.09
Female N (%)	151	134 (88.7)	17 (11.3)	Referent	
Aortic arch position					
Right N (%)	16	14 (4.5)	2 (3.6)	0.82 (0.18,3.73)	0.798
Left N (%)	317	270 (85.2)	47 (14.8)	Referent	
VACTERL association					
Yes N (%)	80	66 (82.5)	14 (17.5)	1.26 (0.65,2.45)	0.492
No N (%)	285	244 (85.6)	41 (14.4)	Referent	
VSD					
Yes N (%)	73	55 (75.3)	18 (24.7)	2.26 (1.2,4.25)	0.012
No N (%)	292	255 (87.3)	37 (12.7)	Referent	
Staged repair					
Yes N (%)	21	13 (61.9)	8 (38.1)	3.89 (1.53,9.89)	0.004
No N (%)	344	297 (86.3)	47 (13.7)	Referent	
Trans-anastomotic tube placement					
Yes N (%)	17	15 (88.2)	2 (11.8)	0.81 (0.18,3.66)	0.786
No N (%)	333	286 (85.9)	47 (14.1)	Referent	
Myotomy					
Yes N (%)	8	8 (100)	0 (0)	N/A	N/A
No N (%)	329	282 (85.7)	47 (14.3)		
Surgical approach					
Thoracoscopy N (%)	79	62 (78.5)	17 (21.5)	2.05 (1.07,3.93)	0.031
Open N (%)	271	23 (88.2)	32 (11.8)	Referent	

SGA: small for gestational age (Olsen 2010), VACTERL association (REF); VSD: ventricular septal defect; N/A = not applicable.



Fig. 1. Receiver operating characteristic (ROC) curve for multivariable model for anastomotic leak.

11–23] days, p < 0.001), older age at PN discontinuation (median 23 [IQR 18–44] vs 14 [IQR 11–20] days, p < 0.001), and increased need for esophageal dilation while inpatient (23 % vs 10 %, p = 0.005). Five of 55 patients with leak (9.1 %) underwent reoperation. Two of the five had an initial open surgery and the other three initially underwent a thoracoscopic operation. Twelve of 310 patients (3.9 %) died in the group without a leak, while 1 of 12 patients (8.3 %) died in the leak group.

4. Discussion

Through CHND, we studied a large, contemporary cohort of patients with type C EA/TEF and analyzed associations between surgical and patient-related factors and the risk for esophageal anastomotic leak. Furthermore, we quantified the impact of anastomotic leak on the short-term outcome of LOS and offer a new tool which enables more precise parental counseling while also quantifying inter-center variation in LOS. These results strongly suggest that centers may have practice differences that contribute to these differential LOS. The 15-fold magnitude of the variation in adjusted



Fig. 2. Kaplan Meier curves for time to inpatient discharge stratified by anastomotic leak.

Table 3

Multivariable Cox proportional hazards model for time to discharge after esophageal anastomosis.

Variable	Unadjusted analysis		Adjusted analysis ^a	Adjusted analysis ^a	
	HR (95 % CI)	Р	HR (95 % CI)	Р	
Leak	0.678 (0.488-0.943)	0.019	0.655 [0.431-0.996]	0.044	
Median birthweight, 100 g	1.001 (1-1.001)	<0.001	1.001 [1.001-1.001]	< 0.001	
SGA <10th centile	0.799 (0.601-1.063)	0.115	1.281 [0.884-1.857]	0.182	
Male gender	1.117 (0.885-1.411)	0.341	1.085 [0.807-1.459]	0.579	
Staged repair	0.429 (0.247-0.743)	0.002	0.771 [0.356-1.667]	0.499	
Thoracoscopic approach	1.195 [0.912 to 1.566]	0.188	1.256 [0.841-1.876]	0.256	
VSD	0.668 [0.499 to 0.894]	0.006	0.849 [0.591–1.22]	0.368	

^a The multivariable model is adjusted for center. See intercenter variation Fig. 3.



Fig. 3. Inter-center variation in adjusted time to hospital discharge. Adjusted hazard ratios (aHRs) for each hospital are presented. Thus, aHRs <1 represent hospitals related to an increased length of hospitalization. The p-value demonstrates differences in aHRs between hospitals.

LOS (independent of leak) between centers suggests that some centers may have opportunities to reduce LOS going forward.

Interestingly, a thoracoscopic approach was associated with increased odds of leak (aOR 3.6, p = 0.011). Other studies have analyzed outcomes based on surgical approach. One study from the Midwest Pediatric Surgery Consortium found no association between surgical approach and leak rate, stricture rate, or length of stay, however those who underwent a thoracoscopic approach were generally healthier (greater weight and gestational age, and lower frequency of congenital heart disease) [5], which suggests that the lack of difference may be a reflection of healthier patients being more likely to have undergone a thoracoscopic approach, and/or that the study was potentially underpowered for that specific outcome. Several meta-analyses of retrospective studies have found that outcomes of thoracoscopic repair are similar or superior to open repair. Benefits of thoracoscopy have included earlier enteral feeding, shorter time to extubation, and shorter length of stay [10–13]. This is the first comparative study that has shown an increased risk of leak in patients undergoing thoracoscopic repair. It is unclear why we observed a greater risk of leak in those undergoing thoracoscopic repairs, further research looking into patient characteristics or surgeon/center volume is warranted.

It is important to emphasize the finding that having an anastomotic leak was associated with increased LOS even after adjusting for patient-related factors and other comorbidities. Many leaks are sub-clinical and self-limiting, and they are often treated by delaying oral feeds until they seal on their own. In our cohort, only 10 % required reoperation due to the presence of a leak, but the presence of a leak was still a contributor to excess LOS. It is important to note, however, that the magnitude of the contribution of leak to LOS was greatly reduced on multivariable analysis after adjusting for SGA, birthweight, VSD, male gender, thoracoscopic

approach, and staged repair, suggesting that patient comorbidities may be driving excess LOS as opposed to the presence or absence of leak. We also found that patients with leak were likely to have greater duration of central lines, longer parenteral nutrition use, and more commonly developed an esophageal anastomotic stricture requiring dilation during their hospital course. The literature has shown that leak is associated with refractory stricture and need for dilation [4]. It is likely that our study underestimates the frequency of stricture development after a leak, as some of these strictures may occur after the index hospitalization. These findings underscore the importance of developing strategies to prevent leak.

In univariate analysis, both birthweight and staged repair were associated with leak. However, in multivariable analysis, staged repair was independently associated with leak while birthweight was not. This finding suggests that leak may be more strongly driven by the increase in complexity that comes with a re-operative field in the setting of a staged repair rather than the small size of the patient at the index operation (TEF repair only), but further investigation is needed to control for selection bias regarding which patients have primary anastomosis versus upfront fistula repair only with delayed esophageal anastomosis. In contrast to our findings, a single center study performed on patients from 1987 to 2008 found that infants born under 1500 g who underwent staged repair versus primary anastomosis had a lower rate of leak and stricture [14]. Our study was not designed to disentangle the relationship between birthweight and staged repair, as it is plausible that lower birth weight may have led to delay in anastomosis, in addition to other factors such as severe congenital heart disease, surgeon, center volume, or experience. With further patient accrual, we anticipate that future studies can clarify the effect of surgical selection biases to address this question.

The association between VSD and anastomotic leak was explored as this was the most common congenital heart defect observed in our analyzed cohort, and its association with leak is novel. The study was not powered to look at lower frequency congenital heart defects, which could be an avenue of future study with further patient accrual in CHND. Other studies have found an association between congenital heart disease and in-hospital mortality [15,16]. We are uncertain of the mechanism behind the greater likelihood of anastomotic leak in patients with VSD. Our data did not capture specific genetic mutation information on each patient; however we speculate that VSD is a marker for additional illness severity and/or patient complexity. These findings require validation in the future with other/larger cohorts.

In patients undergoing thoracotomy, our finding of increased leak rate using a transpleural approach has not previously been reported in the literature and warrants further study. Traditional surgical teaching favors an extrapleural approach not necessarily due to decreased leak rate, but the fact that if there is a leak, there may be a lower risk of mediastinitis and disseminated sepsis since the contamination is confined to the extrapleural space. Additionally, the extrapleural approach may increase success of non-operative management if a leak does occur since the leak is more likely to be contained [17]. One single center study did find that those with an extrapleural approach had success in conservative treatment of anastomotic leak [18], but this study did not have a transpleural comparison group. The decision to choose either transpleural or an extrapleural approach is based on multiple considerations: surgical experience/preference, risk of pleural contamination, anatomic variations, patient conditions, size, and comorbidities, urgency of repair, prior interventions, and likely others. Though our results are reflective of these selection biases, future work can be focused on how these determinants exacerbate/ mitigate the prevalence of post-operative anastomotic leaks.

Center was a significant factor associated with both leak and LOS. As in many studies using CHND, inter-center variations are striking with regard to inpatient outcomes in the NICU [19,20]. Our findings suggest an opportunity to identify high-performing centers in the CHNC and best practices that may be contributing to shorter LOS. Dissemination of best practices across the Consortium should theoretically raise the floor of outcomes for infants with EA/ TEF. Indeed, other clinical outcomes such as timing of oral/enteral feeding, stricture rates, and other variables affecting LOS will need to be considered in this future work as we strive to advance care and improve parental counseling for infants with type C EA/TEF. Given the variability in volume and outcome seen in EA/TEF care, identifying high-performing centers may lead to the consideration of centralization or regionalization of EA/TEF care as is being done in several European countries [21].

This study has several important limitations. As with any manual database, there is the possibility of miscoding, particularly with variables that may have subjective definitions (e.g., long-gap esophageal atresia). Additionally, the surgeon, parents, and ICU teams exhibit selection biases in decision-making, approach, and pre- and post-operative care. While some aspects of this may be accounted for by adjusting for center, many centers in CHNC have multiple surgeons performing EA/TEF repairs, and we are unable to account for potential intrinsic differences between individual surgeons, NICU teams, and other providers. Also, defining a leak can be challenging, as centers may or may not use radiographic studies to define them, and the severity of each leak may be different, but data coordinators used consensus-driven thoughtful variable definitions based on medical record documentation to identify leaks based on both clinical and radiographic characteristics. Currently, the CHNC data does not reliably distinguish between clinical and radiographic anastomotic leaks, and this is an area for future focus. Additionally, CHNC does not collect data on center-specific practices regarding the routine use of a postoperative esophagram after EA/TEF repair. Anecdotally in our discussions with our multi-center, multi-disciplinary teams, routine post-operative esophagrams seem to be a fairly standard, but not universal, practice. Whenever assessing length of stay as an outcome measure, it is important to evaluate rates of readmission, as an early discharge may not always represent high-quality care if it leads to a readmission. Further research should explore rates of readmission in those with and without an esophageal anastomotic leak as well as additional burden within the months following discharge.

5. Conclusion

This analysis lays a foundation for identifying potential modifiable risk factors for adverse outcomes in the type C EA/TEF population. In this large, representative sample of EA/TEF patients treated at level IV NICUs, thoracoscopic approach was identified as a risk factor for leak, and patients with leak were found to have longer LOS and risk of reoperation. This study also highlights the inter-center variation in the incidence of leak and prolonged length of stay in these patients. These findings present opportunities for collaboration with high-performing centers to institute best practices for this vulnerable, complex population and enhance parental counseling.

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39. Seattle Children's Hospital (Robert DiGeronimo, Elizabeth Jacobsen).

40. St. Louis Children's Hospital (Beverly Brozanski, Rakesh Rao). 41. St Paul, Children's Minnesota (Ann Downey).

42. St. Petersburg, All Children's Hospital (Linda Van Marter).

43. Toronto, The Hospital for Sick Children (Kyong-Soon Lee).

44. Washington, Children's National Hospital (Billie Lou Short).

45. Wilmington, Nemours/Alfred I. duPont Hospital for Children (Kevin Sullivan).

46. Winston-Salem, Brenner Children's Hospital (Cherrie Welch).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2024.162015.

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