Journal of Pediatric Surgery 55 (2020) 2356–2361

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Pediatric empyemas – Has the pendulum swung too far?☆

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ARTICLE INFO

Article history:
Received 21 October 2019
Received in revised form 5 December 2019
Accepted 21 December 2019

Key words:
Empyema
Complicated pneumonia
VATS
Fibrinolytics
Fibrinolysis
TPA
Chest tube
Pediatrics
Children
PHIS

ABSTRACT

Background: The management of childhood empyemas has transformed over the past decade, with current trends favoring chest tube placement and intrapleural fibrinolytic therapy. Although this strategy often avoids the need for video-assisted thoracoscopic surgery (VATS), hospital length of stay can be long.
Methods: To characterize national trends and outcomes associated with empyema management, the Pediatric Health Information System (PHIS) database was queried to identify children (2 months–18 years) treated for an empyema between January 2010 and December 2017. The cohort was divided into those treated with primary VATS and those treated with chest tube and intrapleural fibrinolysis. Number of chest radiographic studies obtained, frequency of pediatric intensive care unit (PICU) admission, mechanical ventilation requirements, and length of hospitalization were compared between groups.
Results: A total of 3,365 otherwise healthy children met inclusion criteria. Among them, 523 (16%) were managed with primary VATS and 2,842 (84%) were managed with chest tube and fibrinolytic therapy. Of those who were treated with chest tube and fibrinolysis, 193 (6.8%) subsequently underwent VATS. The percentage of children treated with chest tube and fibrinolysis increased from 65% in 2010 to 95% in 2017 ($p<0.001$). After adjusting for age, race, ethnicity, payer, and region, children who underwent primary VATS received fewer chest radiographic studies, were less likely to be admitted to the PICU or require mechanical ventilation and had a shorter PICU and hospital length of stay compared to those who were treated with chest tube and fibrinolytic therapy ($p<0.001$ for all analyses).
Discussion: Although national trends favor chest tube and fibrinolysis, primary VATS are associated with a shorter hospital and PICU length of stay and a lower requirement for mechanical ventilation. Future studies should aim to risk stratify children who may suffer from a protracted course with the goal to offer primary VATS to this subset of children and return them to normal life more expeditiously.
Level of Evidence: III

Pediatric empyemas can place significant burden on children, families, and the healthcare system. While the overall incidence of childhood pneumonia has declined in recent years, the proportion of those associated with empyemas has risen [1, 2]. Beyond antibiotic therapy, procedural management is often indicated. This includes chest tube insertion, with or without intrapleural fibrinolytic agents, video-assisted thoracoscopic surgery (VATS), and in extreme cases thoracotomy. Within the past decade, three randomized control trials compared chest tube with instillation of a fibrinolytic agent to primary VATS and found similar hospital length of stay (LOS) with reduced total costs in the chest tube and fibrinolysis group [3–5]. Although these studies used two different fibrinolytic agents, the findings were congruent. Consequently, in 2012, the American Pediatric Surgical Association (APSA) Outcomes and Clinical Trials Committee published recommendations supporting chest tube with intrapleural fibrinolysis as the initial management strategy for pediatric empyemas [6]. Despite this report, practice patterns remain quite diverse, and 15-68% of children with an empyema undergo a VATS either at the time of presentation or after a trial of intrapleural fibrinolysis [7–11].

☆ Funding was provided by the Children's Hospital Center for Research in Outcomes in Children's Surgery.
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https://doi.org/10.1016/j.jpedsurg.2019.12.017
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Proponents of chest tube and intrapleural fibrinolysis therapy quote a success rate of greater than 80% with comparable or reduced hospital costs, while those opposed cite a shorter hospitalization with primary VATS [10, 12]. Given this division, we sought to review national practice patterns using the Pediatric Health Information System (PHIS) database. In addition, we compared outcome measures to include number of chest radiologic studies obtained, frequency and duration of pediatric intensive care unit (PICU) admissions and mechanical ventilation, as well as hospital LOS between groups.

1. Methods

Pediatric Health Information System (PHIS) is an administrative database governed by Children's Hospital Association (Overland Park, KS) which contains inpatient, emergency department, ambulatory surgery and observation data from 52 tertiary care pediatric hospitals in the US. Data quality is assured through a joint effort between the Children's Hospital Association and contributing hospitals. Participating hospitals provide discharge/encounter data to include demographics, diagnoses, and procedures as well as utilization data to include pharmaceuticals and imaging information. Data are de-identified and subjected to reliability confirmation prior to database entry.

Children 2 months to 18 years of age admitted between January 2010 and December 2017 were included. The cohort was defined using diagnostic and procedural International Classification of Diseases (ICD) 9/10 codes to identify children diagnosed with pneumonia or pneumonitis who underwent a VATS or had a chest tube placed. Children who were treated with a chest tube alone (e.g. no intrapleural fibrinolytics) and did not undergo a VATS were excluded. Fibrinolytic therapy consisted of tissue plasminogen activator (tPA), urokinase, or streptokinase. As APSA guidelines do not currently provide different recommendations for simple pleural effusions and empyemas in children with complicated pneumonias, we grouped children with effusions into the empyema cohort.

To minimize confounders, children who had unrelated comorbidities, malignancies, end-stage renal disease, a previous transplant, or who were placed on extracorporeal membrane oxygenation (ECMO) were excluded. A list of excluded comorbidities was derived from Feudtner et al. [13]. Children with data quality concerns were also excluded. Fig. 1 provides a flow diagram with the number of patients meeting inclusion and exclusion criteria. Data quality was then confirmed by identifying the total number of patients acquired from PHIS at our institution during two separate years (2012 and 2017) – the first time point reflects a period when ICD9 codes were used and the second when ICD10 codes were used. After institutional review board approval, we then queried our electronic medical records to identify the number of children who met inclusion criteria and compared this value to the PHIS de-identified subjects in each group (chest tube with fibrinolysis and primary VATS). To account for temporal practice changes, we performed subgroup analyses of children cared for between 2010–2013 and 2014–2017.

Demographic and outcome data were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences in groups were compared using chi-squared test for categorical or dichotomous variables and ANOVA for continuous variables. Logistic regressions were used for

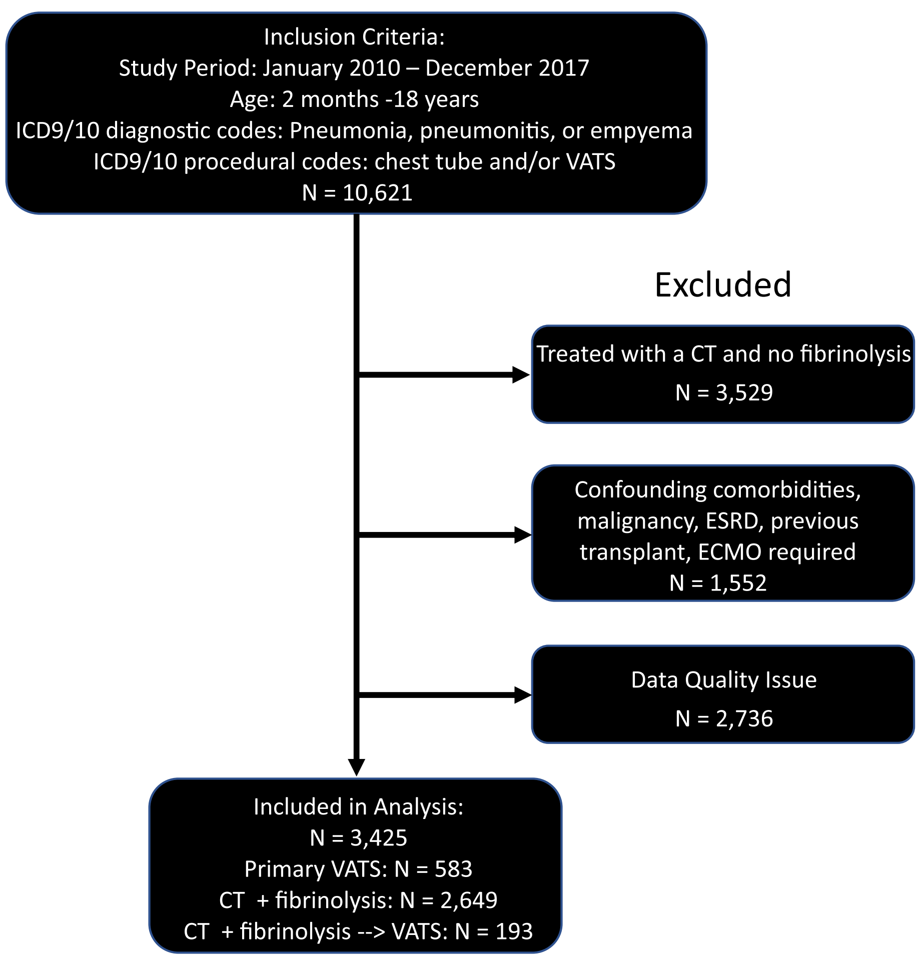

Fig. 1. Flow diagram defining the study cohort. ICD, international classification of diseases; CT, chest tube; ESRD, end-stage renal disease; ECMO, extracorporeal membrane oxygenation; VATS, video-assisted thoracoscopic surgery.

Table 1
Description of cohort.

	Overall (n = 3,425)	Chest tube + fibrinolysis (n = 2,842)	Primary VATS (n = 583)	p-Value
Age (years)	6.78 ± 7.42	6.72 ± 6.73	7.05 ± 10.1	0.4537
Gender				0.5686
Female	1,565 (45.7%)	1,288 (82.3%)	277 (17.7%)	
Male	1,859 (54.3%)	1,553 (83.5%)	306 (16.5%)	
Unknown	1 (0%)	1 (100%)	0 (0%)	
Race				
White	2,134 (62.3%)	1,773 (83.1%)	361 (16.9%)	0.8698
Black	523 (15.3%)	452 (86.4%)	71 (13.6%)	0.0268
Other	663 (19.4%)	554 (83.6%)	109 (16.4%)	0.6994
Ethnicity				0.3441
Hispanic or Latino	736 (21.5%)	600 (81.5%)	136 (18.5%)	
Not Hispanic or Latino	2,349 (68.6%)	1,953 (83.1%)	396 (16.9%)	
Unknown	340 (9.9%)	289 (85%)	51 (15%)	
Payer				<0.001
Government	1,773 (51.8%)	1,506 (84.9%)	267 (15.1%)	
Other	722 (21.1%)	602 (83.4%)	120 (16.6%)	
Private	930 (27.2%)	734 (78.9%)	196 (21.1%)	
Region				<0.001
Midwest	1,102 (32.2%)	1,029 (93.4%)	73 (6.6%)	
Northeast	320 (9.3%)	282 (88.1%)	38 (11.9%)	
South	1,192 (34.8%)	902 (75.7%)	290 (24.3%)	
West	811 (23.7%)	629 (77.6%)	182 (22.4%)	

Data presented as mean ± standard deviation or n (%). *Categorical data within race were analyzed independently as more than one race could be reported. VATS, video-assisted thoracoscopic surgery.

dichotomous outcomes of interest (PICU admission and mechanical ventilation) adjusting for age, race, ethnicity, payer, and region. Generalized linear regression assuming a Poisson distribution was used for the count outcomes of interest (chest radiographic studies, chest tube, number of admissions, LOS, days on mechanical ventilation) also adjusting for the aforementioned confounders. Incidence rates and estimates were exponentiated for interpretability. Statistically significant differences were defined by a p-value of <0.05. Analysis was conducted using R version 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria).

2. Results

2.1. Description of the cohort

Between January 2010 and December 2017, 3,425 otherwise healthy children were admitted for the management of an empyema. Among them, 583 (16%) were managed with a primary VATS and 2,842 (84%) were managed with a chest tube and fibrinolysis. Demographics between the two cohorts are described in Table 1. While age, gender, and ethnicity were not significantly different between the two groups, minor but significant differences were observed between race, payor, and census region.

2.2. Management over Time

In 2010 (first year of this study), 65% of children included in this analysis were initially treated with a chest tube and fibrinolysis. By 2017 (final year of this study), 95% were initially treated with this strategy (p<0.001). Similarly, the frequency of primary VATS decreased from 35% of cases in 2010 to 5.3% of cases in 2017 (p<0.001, Fig. 2). The mean number of fibrinolytic doses was 3.29 ± 2.01 with 29% of children receiving fibrinolytic therapy beyond three days. Progression to VATS after chest tube and fibrinolysis varied between 4.1% and 9.2%, depending on the year. No significant difference between the rate of

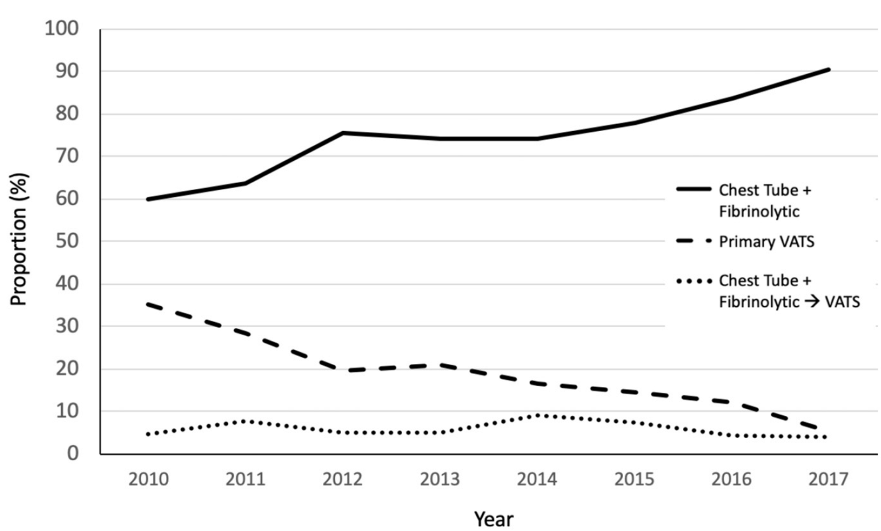

Fig. 2. National practice trends over time.

Table 2
Unadjusted outcomes by treatment strategy.

	Overall (n = 3,425)	Chest tube + fibrinolysis (n = 2,842)	Primary VATS (n = 583)	p-Value
Radiography				
Chest X-ray	11.9 ± 9.06	12.4 ± 9.26	9.63 ± 7.51	<0.001
Chest CT	0.59 ± 0.79	0.58 ± 0.80	0.61 ± 0.74	0.123
Length of stay	17.3 ± 12.8	17.9 ± 13.2	14.0 ± 9.77	<0.001
PICU admission	2,071 (60.5%)	1,820 (64.0%)	251 (43.1%)	<0.001
PICU days	7.49 ± 11.1	8.38 ± 11.6	3.19 ± 7.23	<0.001
Mechanical ventilation	1,105 (32.3%)	960 (33.8%)	145 (24.9%)	<0.001
Mechanical ventilation days	3.52 ± 7.86	3.97 ± 8.37	1.33 ± 3.98	<0.001

Data presented as mean (standard deviation) or n (%). VATS, video-assisted thoracoscopic surgery; X-Ray, radiograph; CT, computer topography; PICU, pediatric intensive care unit.

Table 3
Adjusted shorter-term outcomes.

	Ratio primary VATS Compared to chest tube + fibrinolysis	95% CI	p-Value
Radiography			
Chest X-ray	0.78	0.75 – 0.80	<**0.001**
Chest CT	1.14	1.00 – 1.29	**0.042**
Length of stay	0.77	0.75 – 0.78	<**0.001**
PICU admission*	0.43	0.35 – 0.52	<**0.001**
PICU days	0.37	0.36 – 0.39	<**0.001**
Mechanical ventilation*	0.59	0.47 – 0.72	<**0.001**
Mechanical ventilation days	0.32	0.30 – 0.34	<**0.001**

Ratios reflect rate ratios for Poisson distribution and odds ratios for binomial data and were adjusting for age, race, ethnicity, payer, and region. * Indicates logistic regression (all other models were generalized linear models using a Poisson distribution). VATS, videoassisted thoracoscopic surgery; CI, confidence interval; X-Ray, radiograph; CT, computer topography; PICU, pediatric intensive care unit.

progression to VATS was observed between 2010 and 2017 (4.7% vs 4.1%, respectively, p = 0.941).

2.3. Short-term outcomes

The mean duration of hospitalization for the entire cohort was 17 days. A PICU admission was indicated in 59.2% of children and 39.1% were placed on mechanical ventilation. The mean number of chest radiographs was 11.9 ± 9.06 per child and at least one chest CT was obtained in 1,507 (44%) children. Other than the mean number of chest CTs per child, which was similar between groups, all other outcome variables including chest radiographs, frequency and duration of PICU admissions and mechanical ventilation requirements, were fewer among children who underwent primary VATS (Table 2). After adjusting for age, race, ethnicity, payer, and region, differences remained significant. LOS was reduced by 23% and PICU admissions were reduced by 57% among children who underwent primary VATS. The total number of days admitted to the PICU and the need for mechanical ventilation was also significantly more favorable among those who underwent primary VATS (Table 3).

To account for disease severity, we adjusted for need for supplemental oxygen and mechanical ventilation as well as hospital length of stay prior to a child's first intervention. The remaining outcomes then included frequency of PICU admissions, which again was fewer among those who underwent primary VATS (ratio 0.46, CI 0.36–0.59). PICU length of stay was also significantly shorter among those who underwent primary VATS (ratio 0.61, CI 0.58–0.64). Radiographically, no difference was observed between the number of chest radiographs between the two groups (radio 0.98, CI 0.95-1.01) but children who underwent primary VATS were more likely to receive a chest CT (ratio 1.27, CI 1.12-1.44).

2.4. Progression to VATS

Among children treated with chest tube and fibrinolysis, 193 (6.8%) subsequently underwent a VATS. Compared to those who underwent primary VATS or who were successfully treated with a chest tube and fibrinolysis, children who failed fibrinolysis and progressed to VATS received more chest radiographic studies, were more likely to require mechanical ventilation, and have a longer PICU and hospital LOS (p<0.001 for each variable, Table 4).

2.5. Subgroup analysis to account for practice shifts over time

As this study analyzed outcomes from 2010 and 2017, a period during which national practice patterns shifted drastically, we divide the cohort into an early and late group and performed two separate subgroup analyses. The purpose of this analysis was to determine if the outcomes from the entire cohort align with outcomes observed in the new era of empyema management. Aside from percent of patients requiring mechanical ventilation, which was similar between the primary VATS and chest tube and fibrinolysis groups, all other outcome measures were significantly better in the primary VATS group within the 2014–2017 sub-group analysis, mirroring the results reported for the entire cohort (Table 5). As a correlate, we also compared outcomes

Table 4
Outcomes including children who progressed from chest tube + fibrinolysis to video-assisted thoracoscopic surgery.

	Chest tube + fibrinolysis (n = 2,649)	Primary VATS (n = 583)	Chest tube + fibrinolysis → VATS (n = 193)	p-Value
Radiography				
Chest X-ray	12.1 ± 9.21	9.63 ± 7.51	15.9 ± 9.20	<0.001
Chest CT	0.55 ± 0.77	0.61 ± 0.74	1.12 ± 1.02	<0.001
Length of stay	17.7 ± 13.3	14.0 ± 9.77	21.2 ± 12.2	<0.001
PICU admission	1,663 (62.8%)	251 (43.1%)	157 (81.3%)	<0.001
PICU days	8.26 ± 11.6	3.19 ± 7.23	10.0 ± 11.4	<0.001
Mechanical ventilation	885 (33.4%)	145 (24.9%)	75 (38.9%)	<0.001
Mechanical ventilation days	3.99 ± 8.43	1.33 ± 3.98	3.76 ± 7.52	<0.001

Data presented as mean ± standard deviation or n (%). VATS, video-assisted thoracoscopic surgery; X-Ray, radiograph; CT, computer topography; PICU, pediatric intensive care unit.

Table 5
Unadjusted outcomes by treatment strategy and time period.

Time period: 2010-2013	Overall (n = 1,614)	Chest tube + fibrinolysis (n = 1,441)	Primary VATS (n = 173)	p-Value
Radiography				
Chest X-ray	12.0 ± 9.30	13.0 ± 9.87	8.99 ± 6.53	<0.001
Chest CT	0.63 ± 0.79	0.64 ± 0.81	0.61 ± 0.74	0.633
Length of stay	16.8 ± 12.5	18.2 ± 13.4	13.2 ± 8.86	<0.001
PICU admission	789 (56.2%)	640 (63.6%)	149 (37.5%)	<0.001
PICU days	7.11 ± 11.4	8.90 ± 12.3	2.57 ± 6.47	<0.001
Mechanical ventilation	408 (29.1%)	324 (32.2%)	84 (21.2%)	<0.001
Mechanical ventilation days	3.17 ± 7.76	4.03 ± 8.79	1.00 ± 3.30	<0.001
Time period: 2014–2017	Overall (n = 1,404)	Chest tube + fibrinolysis (n = 1,007)	Primary VATS (n = 397)	p-Value
Radiography				
Chest X-ray	12.1 ± 9.24	12.3 ± 9.25	10.7 ± 9.08	0.008
Chest CT	0.55 ± 0.78	0.55 ± 0.78	0.60 ± 0.73	0.141
Length of stay	17.8 ± 13.3	18.1 ± 13.4	15.4 ± 11.4	0.037
PICU admission	1,018 (63.1%)	930 (64.5%)	88 (50.9%)	<0.001
PICU days	7.97 ± 11.4	8.41 ± 11.6	4.25 ± 8.55	<0.001
Mechanical ventilation	557 (34.5%)	505 (35.0%)	52 (30.1%)	0.223
Mechanical ventilation days	3.92 ± 8.31	4.17 ± 8.59	1.84 ± 5.02	0.019

Data presented as mean (standard deviation) or n (%). VATS, video-assisted thoracoscopic surgery; X-Ray, radiograph; CT, computer topography; PICU, pediatric intensive care unit.

among children in the early group (2010-2013) and found all measures to be significantly better among those who underwent primary VATS.

3. Discussion

Over the past eight years, the pendulum has shifted away from primary VATS and toward chest tube placement with intrapleural fibrinolysis. In fact, 95% of pediatric empyemas in the US were initially managed with a chest tube and intrapleural fibrinolysis in 2017. While this strategy has proven to be effective, with only 7% of cases progressing to VATS, we found that primary VATS was associated with less chest radiation exposure, a shorter duration of mechanical ventilation if indicated, and fewer days admitted to the PICU and hospital than chest tube and fibrinolysis therapy. These findings beg the question of whether we have swung the pendulum too far.

Evident by our findings and the APSA Outcomes and Clinical Trials Committee recommendations, a majority of providers in the US favor chest tube and fibrinolysis as the initial management for pediatric empyemas. Randomized control trials demonstrating that in single institutions well versed in intrapleural fibrinolysis, hospital LOS is similar to that of primary VATS while hospital charges are reduced [4, 5, 14]. Furthermore, St. Peter et al. reported no difference in days febrile, duration of supplemental oxygen requirement and doses of narcotics between the two treatment groups [5]. Contrasting these results, we found an increased LOS and use of healthcare resources including mechanical ventilation and radiologic studies. Perhaps with national implementation of specialized protocols aimed to standardize fibrinolytic therapy we would have found similar outcomes between groups, however, we were unable to evaluate for this factor in the current study.

Independent of the management strategy chosen, caring for pediatric empyemas is expensive. While it has been reported that fibrinolytic therapy cost less than VATS by 35% [5], other studies utilizing billing data found that median hospital charges were similar between groups ($32,136 for VATS and $36,618 for chest tube and fibrinolysis, $p = 0.401$). The authors of this study concluded that the cost of VATS is offset by the higher need for further procedures and longer hospital LOS in the chest tube and fibrinolysis group [15]. This observation is further supported by several studies that suggest length of hospitalization is shorter among those who undergo primary VATS [16–18]. In a pooled meta-analysis of seven trials including 231 patients (both children and adults), Redden et al. concluded that the mean length of hospitalization was significantly shorter among those who underwent primary VATS. However, in a subgroup analysis including only children, the mean difference was 1.99 days fewer in the primary VATS group, but this did not reach statistical significance [19]. While we did not directly compare billing data between groups in the current analysis, we surmise that the shorter hospital LOS likely offsets the additional expense associated with a surgical procedure.

Conflicting reports exist regarding failure rates associated with each strategy. Cohen et al. reported that the failure rate associated with both fibrinolysis and primary VATS is approximately 10% [20]. Additional studies quote a slightly higher failure rate of approximately 15% associated with chest tube and fibrinolysis [4, 5, 21]. We found the failure rate to be less than 10%. While this disparity is not entirely clear, these publications preceded the study period in this report, and it is possible that some institutions have become more experienced and persistent with fibrinolysis therapy and continue this strategy beyond three days with the hope of avoiding VATS. This argument is supported by the fact that 29% of patients received greater than three days of a fibrinolytic agent.

While predictors of failed intrapleural therapy have been reported, including pleural thickening, presence of an intraparenchymal abscess, or necrotizing pneumonia, this cohort is poorly defined [21, 22]. Perhaps by identifying those who are likely to fail fibrinolysis, we can stratify the population that may benefit from primary VATS. As PHIS does not capture clinical data such as vital signs and laboratory values, we were unable to identify markers to predict fibrinolysis failure. Future studies should focus to identify those who are likely to fail chest tube and fibrinolysis therapy. By managing children based on predictors of fibrinolysis failure, outcomes between the two groups may become more closely aligned.

This study has several potential limitations. As PHIS is an administrative database, the potential for inaccurate reporting exists. To minimize this shortcoming, we exclude children with data quality issues and cross-referenced our institutional cohort numbers provided by PHIS to our electronic medical records to confirm concordance. Additionally, the cohort of children who develop pneumonia is heterogeneous and underlying conditions such as cystic fibrosis may have skewed our results. We therefore limited this study to otherwise healthy children excluding children with significant comorbidities which was feasible given the large sampling. An additional limitation was our inability to stratify the cohort based on disease severity. Dorman et al., who also evaluated national trends in the management of pediatric empyemas using the PHIS database, used need for mechanical ventilation as a surrogate for disease severity [9]. In an attempt to account for disease severity, we performed an additional analysis adjusting for need for supplemental oxygen and mechanical ventilation as well as hospital length of stay prior to a child's first intervention. The remaining outcome variables, PICU admissions and PICU length of stay, continued to favor primary VATS.

The results from this study suggest that an equipoise between non-operative and operative strategies should be found to offer best practice guidelines for the management of pediatric empyemas. While it has been well established that chest tube and fibrinolytic therapy play a central role in managing of empyemas, a multi-institutional randomized control trial stratifying children by disease severity is warranted. Additional research should also focus on identifying risk factors for fibrinolytic failure with the goal to offer primary VATS to this subset of children and return them to normal life more expeditiously.

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