

Pediatric Thoracic Empyema—Outcomes of Intrapleural Thrombolytics: Ten Years of Experience

Global Pediatric Health
Volume 7: 1–7
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2333794X20928200
journals.sagepub.com/home/gph



Aram Baram, MD, MRCSEd, FACS, AFSCTS¹  and Fitoon Yaldo, MBChM²

Abstract

Introduction. Pediatric thoracic empyema is a special entity with increasing frequency. Consensus regarding the best management strategy is still evolving. We describe our single-center 10-year experience adopting intrapleural thrombolytics using tissue plasminogen activator as first-line treatment following failure of simple thoracostomy drainage techniques. **Methods.** Observational prospective study included all children from 1 day to 18 years admitted for parapneumonic effusion and treated with intrapleural thrombolytics. **Results.** From January 2008 to December 2018, 95 patients were treated by intrapleural thrombolytics for different stages of empyema thoracis. Number of thrombolytic doses required is 2.1 (range = 1-3), and mean amount of drainage is 1050 mL (range = 400-2500 mL). Mean total days of hospitalization is 7.3 days. Complete re-expansion was the primary outcome in 94 patients (98.9%). **Conclusion.** Intrapleural thrombolytics in complicated pediatric thoracic empyema results in excellent outcome and should be encouraged particularly in limited resource countries.

Keywords

Pediatric Thoracic empyema, thrombolytic therapy, short term outcome, long-term outcome

Received January 13, 2020. Received revised March 31, 2020. Accepted for publication April 13, 2020.

Introduction

Empyema thoracis occurs in children when parapneumonic effusion complicates pulmonary parenchymal infection resulting in accumulation of exudative fluid in the pleural space followed by fibrin deposition, which if not properly treated would eventually form an inelastic peel that inhibits lung from proper expansion.¹

A meta-analysis performed by Avansino et al showed that approximately 1 out of 150 children admitted for pneumonia only would develop empyema, at an incidence between 0.4 and 6 cases per 1000 pediatric admissions.² Giving an approximate incidence of 0.6% to 2% of pediatric pneumonia cases to be complicated by empyema.³

Though its well-known that the infection process occurs in a continuum and not distinctly, pediatric thoracic empyema (PTE) has been classified into 3 different stages: (1) exudative or simple parapneumonic effusion, where there is only clear pleural fluid; (2) fibrinopurulent stage, where the fibrin starts to deposit

forming septations and loculations within which the fluid is still flowing freely; and (3) organizing phase, where the fluid would be infiltrated by fibroblast and the thin intrapleural membranes changes to thick nonelastic peel resulting in impairment of lung function.¹⁻⁴

Currently, management of pediatric empyema is dependent on local practice guidelines and physician preference as there is no standardized treatment regimen for PTE yet. This might be due to a deficiency of pediatric-based and population-based evidence.^{4,5}

Sixty-nine years ago, use of fibrinolytics was described in the management of complex pleural process by

¹University of Sulaimani, Sulaymaniyah, Kurdistan, Iraq

²Kurdistan Board for Medical Specialties, Erbil, Kurdistan Region, Iraq

Corresponding Author:

Aram Baram, Department of Thoracic and Cardiovascular Surgery, University of Sulaimani, François Mitterrand Street, Sulaymaniyah, Kurdistan 46001, Iraq.

Email: aram.baramm@gmail.com; aram.baram@univsul.edu.iq



Tillet and Sherry when they introduced streptokinase. Ever since, the use of streptokinase as a thrombolytic agent was taxing because of the possibility of antibodies' development and the occurrence of delayed hypersensitivity reaction. This led to the introduction of urokinase to minimize the aforementioned complications associated with streptokinase. Withdrawal of urokinase from markets by the Food and Drug Administration in the United States because of infection risks led to the emergence of alteplase in 2000. The use of intrapleural thrombolytics in certain patients has been stated by many authors despite the controversies about many aspects.⁴⁻⁶

In spite of the breakthrough in antibiotics therapy in the latest era, parapneumonic effusion and pleural empyema are still a frequent clinical problem that may cause significant mortality and morbidity. The well-established treatment for parapneumonic effusions is drainage by closed system tube drainage and systemic antibiotics.^{3,7} However, the latter can be associated with failure rate as high as 40% in addition to increased hospital stay duration.^{2,8} Surgical intervention becomes mandatory when the infection and sepsis are not adequately controlled by tube thoracostomy. In multiloculated pleural effusion and empyema, installation of a thrombolytic agent like tissue plasminogen activator has been broadly described for ease of lysis of the fibrinous loculi.^{5,7,8} Despite many studies describing outcomes of intrapleural thrombolytics in pediatric empyema thoracis, the current literature is still deficient in randomized control trials about this subject, which has led to controversial evidence in support for the use of this approach.⁵⁻⁸ In this article, we discuss our 10 years of experience in the outcome of using intrapleural thrombolytics for pediatric patients with thoracic empyema.

Patients and Methods

Patient Selection

Observational prospective clinical cohort study included all children aged from 1 day to 18 years, admitted consecutively for treatment of parapneumonic effusions by tube thoracostomy of appropriate size and length (14-28 French) combined with intrapleural instillation of thrombolytics in a single center. Other causes for pleural effusion such as tuberculosis and malignant effusions were excluded.

From January 2008 to January 2018, 95 patients were treated by intrapleural thrombolytics for different stages of empyema thoracis. Tissue plasminogen activator (Actilyse, Boehringer Ingelheim) 0.1 mg/kg/dose mixed in 10 to 30 mL of normal saline was instilled through the

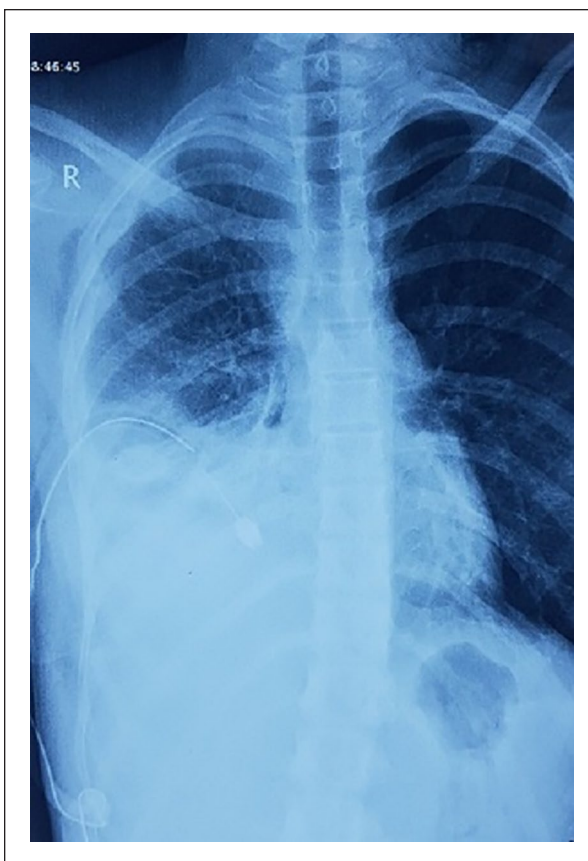


Figure 1. Chest X-ray shows right side parapneumonic effusion with a chest tube inserted and minimal amount of drainage after 2 days.

tube thoracostomy followed by clamping of the chest tube for 4 hours. Patient's mobilization is encouraged during and after the clamping period to allow better distribution of the chemical agent and for enhancing drainage after de-clamping.

There were 50 females (52.6%) and 45 males (47.4%). Mean age was 6.3 years (range = 0.5-15). Regarding empyema stages, 86 patients (90.5%) were in stage 2, 5 patients (5.3%) were in stage 3, and 4 patients (4.2 %) were in stage 1.

Mean number of thrombolytic doses required was 2.1 (range = 1-3), with a mean amount of drainage 1050 mL (range = 400-2500).

The patients were followed-up clinically and radiological by serial chest X-rays (CXR; Figure 1) for 1, 2, 3, 6, 12, 18, and 24 months and continued to 3 and 5 years.

The focus was pointed on in hospital course, 1-month follow-up (primary outcome), and 1 year (secondary outcome).

Table 1. Number of Doses and Amount Drainage Distribution of Patients Studied.

	Gender		Total (n = 95)
	Female (n = 50)	Male (n = 45)	
Number of doses			
1	11 (22%)	10 (22.2%)	21 (22.1%)
2	23 (46%)	20 (44.4%)	43 (45.3%)
3	16 (32%)	15 (33.3%)	31 (32.6%)
Amount of drainage (mL)			
< 1000	25 (50%)	20 (44.4%)	45 (47.4%)
1000-1800	25 (50%)	23 (51.1%)	48 (50.5%)
> 1800	0 (0%)	2 (4.4%)	2 (2.1%)

Table 2. Number of Doses.

Number of doses	Provisional stage			Total
	Stage 1	Stage 2	Stage 3	
1	0 (0%)	21 (24.4%)	0 (0%)	21 (22.1%)
2	4 (100%)	37 (43%)	2 (40%)	43 (45.3%)
3	0 (0%)	28 (32.6%)	3 (60%)	31 (32.6%)
Total	4 (100%)	86 (100%)	5 (100%)	95 (100%)

Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. The statistical software SPSS (22.0) and R (ver. 3.2.2) were used for the analysis of the data, and Microsoft Word and Excel were used to generate graphs, tables, and so on. Suggestive significance was when P value was $<.05 < P <.10$; moderately significant when P value was $<.01 < P \leq .05$; and strongly significant when P value was $P \leq .01$.

Ethical Approval and Informed Consent

Informed consent and consent for publication was obtained from all parents of the participating children. Ethical approval was obtained from the Ethical Committee of Kurdistan Board for Medical Specialization (Approval Number: 346, August 7, 2018).

Results

A total of 95 (50 females and 45 males) pediatric patients were treated by intrapleural Actilyse, over 10 years. The right hemithorax was involved in 60 patients (63.2%), while the left side was involved in 35 patients (36.8%).

Mean age was 6.3 years (range = 0.5-15), mean hemoglobin concentration was 11.5 g/dL (range = 8-15), mean white blood cells count was 16835.8 cells/L

(range = 1500-30 000), and mean erythrocyte sedimentation rate was 81 mm/h (range = 40-110).

There were 86 patients (90.5%) in stage 2, 5 patients (5.3%) in stage 3, and 4 patients (4.2%) in stage 1. Mean number of thrombolytic doses required is 2.1 (range = 1-3), and mean amount of drainage is 1050 mL (range = 400-2500 mL). Mean total days of hospitalization is 7.3 days (range = 1-21 days). Table 1 shows number of doses and amount of drainage distribution of patients studied, and Table 2 shows number of thrombolytic doses required in relation to the provisional stage of empyema. Table 3 shows comparison of study variables according to provisional stage of patients studied.

In 93 patients (97.9%) the presenting symptom was shortness of breath, 91 patients (95.8%) had fever, 55 patient (57.9%) had history of weight loss, 50 patients (52.6%) had dry cough, 45 patients (47.4%) had productive cough, 31 patients (32.6%) had vomiting, 26 patients (27.4%) were not feeding properly, 23 patients (24.2%) had hemoptysis, diarrhea was present in 21 patients, chest pain was present in 21 patients (22.1%), 10 patients (10.5%) had failure to thrive, 2 patient (2.1 %) were accidentally diagnosed, and 1 patient (1.1 %) had stridor.

On physical examination, all patients had unilateral decreased air entry and wheezes (100%), whereas bilateral decreased air entry were found in only 44 patients

Table 3. Comparison of Study Variables According to Provisional Stage of Patients Studied.

Variables	Provisional stage			Total	P
	Stage 1	Stage 2	Stage 3		
Amount of drainage (mL)	1050.00 ± 100.00	1037.79 ± 356.28	1260.00 ± 343.51	1050.00 ± 350.15	.390
Total days of hospitalization	8.75 ± 2.22	7.28 ± 3.21	7.80 ± 6.38	7.37 ± 3.36	.669
Hemoglobin (g/dL)	11.50 ± 1.29	11.55 ± 1.60	11.3 ± 1.64	11.54 ± 1.58	.940
WBC (cells/L)	15250.00 ± 957.43	16725.58 ± 5427.84	20000.00 ± 4062.02	16835.79 ± 5293.65	.339
CRP (mg/dL)	91.25 ± 8.54	95.15 ± 80.08	80.00 ± 21.51	94.19 ± 76.37	.910
ESR (mm/h)	75.00 ± 17.32	81.74 ± 14.09	75.00 ± 22.91	81.11 ± 14.68	.428

Abbreviations: WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.



Figure 2. The same patient chest X-ray after 1 month from thrombolytic therapy shows minimal right costophrenic angle obliteration with mild right lung entrapment.

(46.3%), bronchial breathing were found in 90 patients (94.7%), cervical lymphadenopathy was found in 35 patients (36.8%), and organomegaly was found in only 2 patients (2.1%).

On CXR, 92 patients (96.9%) had pleural effusion (Figure 1), 3 patients (3.2%) had non-homogenous opacity, and 2 patients (2.1%) had multiple air fluid level. Computed tomography was requested in only 5 cases (5.4%); of those, 3 patients (3.2%) had thick effusion, 1 patient (1.1 %) had bilateral cavity lesion, and 1 patient (1.1%) had loculated pleural effusion. In 79 patients (83.2%), *Streptococcus pneumoniae* was the causative microorganism found in the fluid culture and

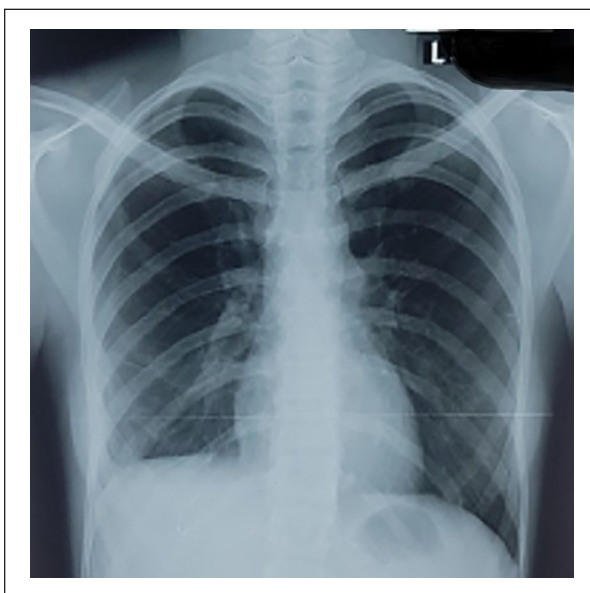


Figure 3. Chest X-ray at 1 year from thrombolytics shows near-normal lung expansion.

sensitivity, in 7 patients (7.4%) *Staphylococcus aureus* was responsible, 5 patients (5.3%) had *Haemophilus influenzae*, and 4 patients (4.2%) had *Pseudomonas aeruginosa*.

Ninety-four patients (98.9%) had total re-expansion as a primary (in hospital) outcome, no signs of lung expansion was seen in only 1 patient (1.1%), who was a 7-year-old male child, with right side involvement, despite 3 doses of thrombolytic and 1100 mL drainage, who recovered well after decortication with good lung re-expansion and no signs of fibrothorax on follow-up. Of the patients who showed total re-expansion in the hospital, after only 1 dose of thrombolytics, at the second month of follow-up signs of moderate fibrothorax started to develop on CXR, ended by decortication at the third month of follow-up.

Table 4. Comparison of Primary Outcome at 1 Month Versus Secondary Outcome at 12 Months^a.

Outcome	Primary outcome at 1 month (n = 95)	Secondary outcome at 12 months (n = 95)	% Difference
Total re-expansion	1 (1.1%)	0	-1.1
Basal haziness	16 (16.8%)	0	-16.8
Residual effusion	4 (4.2%)	0	-4.2
obliterated costophrenic angle	63 (66.3%)	6 (6.3%)	-60.0
Mild fibrothorax	1 (1.1%)	2 (2.1%)	1.0
Asthma-like symptoms	0	2 (2.1%)	+2.1
Normal	10 (10.5%)	85 (89.5%)	79.0

^aP < .001, significant, paired proportion test, 79.0% improvement.

At 1-month follow-up (primary outcome; Figure 2), 63 patients (66.3%) had obliterated costophrenic angle, 16 patients (16.8%) had basal haziness, 11 patients (11.6%) had normal looking CXR, 4 patients (4.2%) had residual effusion, and 1 patient (1.1%) had mild fibrothorax.

At 1-year follow-up, 85 patients (89.4 %) had normal looking CXR (Figure 3), 6 patients (6.3%) had obliterated costophrenic angle, 2 patients (2.1%) had mid fibrothorax, and 2 patients (2.1%) had asthma-like symptoms.

Comparison between primary and secondary outcome revealed a $P < .001$ in favor of 79.0% improvement (Table 4).

Discussion

Empyema thoracis in pediatric population is a remarkable factor for morbidity but not mortality, and can represent a therapeutic dilemma; however, so far there is a limited consensus regarding its management, partly due to deficient data from pediatric trials and second due to the inconvenience of applying adult data to pediatric population. The fundamental difference between the 2 groups is the rarity for underlying lung disease in children in contrast to adult favoring the almost always excellent prognosis in the pediatric group treated for empyema as described by the British Society for Thoracic Surgeons guidelines in 2005.⁴ However, the reason behind why some healthy children develop empyema and others not is still not clear; perhaps future studies will show genetic predisposition behind that.⁸

The 2 ancient pillars for management of empyema thoracis are antibiotics and tube thoracostomy drainage of the purulent fluid.⁹ Following this approach alone could lead to prolonged hospital stay and high rate of unsuccessful treatment in advanced stage of this clinical entity. Therefore, the need for a more effective yet less invasive management modality than thoracotomy had led to the introduction of intrapleural thrombolytics and video-assisted thoracoscopic (VATS) debridement

or decortication. The aim of all modalities remain the same in breaking the septations, liquefaction of the fibrinous material aiming at restoring the near-normal lung functions.¹⁰ Comparable outcomes of VATS and intrapleural thrombolytics have been stated by various pediatric trials.^{3,11}

Hanson et al¹⁰ studied the effectiveness of alteplase as an intrapleural fibrinolytic agent in pediatric population, and their results showed significant increase in pleural fluid output on irrigation with alteplase, as they stated this was due to volumetric decrease of the intrapleural fluid and not due to inflammatory reaction as previously was postulated.¹⁰

Despite the relatively few consensus regarding management of pediatric empyema thoracis, the most recent published ones, such as the position statement from the Thoracic Society of Australia and New Zealand and the British Thoracic Society guidelines for the management of pleural infections in children, are strongly recommending the use of intrapleural thrombolytic agents with a clear benefit of shortening hospital stay. In addition to the strong advices against standard open thoracotomy as a first-line management, this latter option is only reserved for case of failure of thrombolytic trial and limited expertise in VATS surgery.^{8,4,12,13,14}

In developing countries, choosing the best treatment modality relies on the existing expertise and common local practices. Currently, we are lacking randomized control trials from developing nations to assess the efficacy of intrapleural thrombolytics versus VATS. Nonetheless, in economically and resource-challenged countries, in which empyema thoracis is not infrequent, utilization VATS require and add to the load of the operative waiting lists, cost, and intensive care units.^{11,14} The fact that in majority of such countries including ours, even the availability of a dedicated pediatric intensive care is a concern and this in turn precludes and discourages adopting VATS decortication for PTE.

Unlike most of published studies where urokinase has been more clinically studied, we presented our

experience with alteplase (Actylase) being the thrombolytic agent available.

The commonest microorganism continues to be *Streptococcus pneumoniae*; however, there might be differences in developed countries where pneumococcal vaccines is being routinely used. In our series, we had 4 patients with *Pseudomonas aeruginosa* as the culprit microorganism, which is a rare cause of community-acquired pneumonia in healthy children,^{10,14} and one of those children had a total hospital stay of 14 days but otherwise good outcome.

Of a total 95 patients, only 2 patients required decortication, one of them during the initial hospital course with failure of lung re-expansion after thrombolytic and the other at 3 months of follow-up, which stands firm with others' opinion to encourage the usage of intrapleural thrombolytics in management of PTE.

Conclusions

Pediatric thoracic empyema is a special entity with growing frequency, and adult guidelines should not be applied to this entity.

Management with tissue plasminogen activator (Actylase) has a good success rate and should be always considered prior to thoracoscopic or open surgical intervention.

Limitation

The study is limited to a relatively small sample size and single-center experience.

Future Research

More studies need to be done in this field to help establish a global guideline in the management of thoracic empyema in children.

Acknowledgments

We would like to acknowledge all our personnel who assisted in serving our patients. Also, we would like to appreciate the great efforts of Dr K. P. Suresh, Scientist (Biostatistics), National Institute of Veterinary Epidemiology and Disease Informatics (NIVEDI), Bangalore 560024, India, in analysis of our raw data.

Author Contributions

Aram Baram: Surgeon in charge, study design, follow-up, data collection, manuscript revision, and statistical analysis. Fitoon Falah Yaldo: Assisted in surgeries, follow-up, study design, data collection, and drafting.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

This study was approved by the Ethics and Scientific Committees of Kurdistan Board for Medical Specialization (Approval Number: 364, August 7, 2018).

Informed Consent

Written consent obtained from all participants that their operation photos and images may be used for scientific publications only.

ORCID iD

Aram Baram  <https://orcid.org/0000-0001-9217-1189>

References

1. Long AM, Smith-Williams J, Mayell S, Couriel J, Jones MO, Losty PD. "Less may be best"—pediatric parapneumonic effusion and empyema management: lessons from a UK center. *J Pediatr Surg*. 2016;51:588-591. doi:10.1016/j.jpedsurg.2015.07.022
2. Avansino JR, Goldman B, Sawin RS, Flum DR. Primary operative versus nonoperative therapy for pediatric empyema: a meta-analysis. *Pediatrics*. 2005;115:1652-1659.
3. Marhuenda C, Barceló C, Fuentes I, et al. Urokinase versus VATS for treatment of empyema: a randomized multicenter clinical trial. *Pediatrics*. 2014;134:e1301-e1307. doi:10.1542/peds.2013-3935
4. Slaats MA, De Dooy J, Van Hoorenbeeck K, Van Schil PEY, Verhulst SL, Hendriks JMH. A combined intrapleural administration of dornase alfa and tissue plasminogen activator is safe in children with empyema—a pilot study [published online December 3, 2019]. *Acta Chir Belg*. doi:10.1080/00015458.2019.1696516
5. Balfour-Lynn IM, Abrahamson E, Cohen G, et al. BTS guidelines for the management of pleural infection in children. *Thorax*. 2005;60(suppl 1):i1-i21.
6. Course CW, Hanks R, Doull I. Question 1. What is the best treatment option for empyema requiring drainage in children? *Arch Dis Child*. 2017;102:588-590. doi:10.1136/archdischild-2017-312938
7. Ben-Or S, Feins RH, Veeramachaneni NK, Haithcock BE. Effectiveness and risks associated with intrapleural alteplase by means of tube thoracostomy. *Ann Thorac Surg*. 2011;91:860-863. doi:10.1016/j.athoracsur.2010.10.082

8. Nie W, Liu Y, Ye J, et al. Efficacy of intrapleural instillation of fibrinolytics for treating pleural empyema and parapneumonic effusion: a meta-analysis of randomized control trials. *Clin Respir J*. 2014;8:281-291. doi:10.1111/crj.12068
9. Strachan RE, Jaffé A; Thoracic Society of Australia and New Zealand. Recommendations for management paediatric empyema thoracis. *Med J Aust*. 2011;195:95.
10. Hanson SJ, Havens PL, Simpson PM, Nugent ML, Wells RG. Intrapleural alteplase decreases parapneumonic effusion volume in children more than saline irrigation. *Pediatr Pulmonol*. 2015;50:1328-1335. doi:10.1002/ppul.23184
11. Chen SM, Sheu JN, Chen JP, Yang MH. Community-acquired *Pseudomonas aeruginosa* pneumonia complicated with loculated empyema in an infant with selective IgA deficiency. *Acta Paediatr Taiwan*. 2002;43:157-161.
12. Shankar G, Sahadev R, Santhanakrishnan R. Pediatric empyema thoracis management: should the consensus be different for the developing countries? *J Pediatr Surg*. 2020;55:513-517. doi:10.1016/j.jpedsurg.2019.08.009
13. Stefanutti G, Ghirardo V, Barbato A, Gamba P. Evaluation of a pediatric protocol of intrapleural urokinase for pleural empyema: a prospective study. *Surgery*. 2010;148:589-594. doi:10.1016/j.surg.2010.01.010
14. Petel D, Li P, Emil S. Percutaneous pigtail catheter versus tube thoracostomy for pediatric empyema: a comparison of outcomes. *Surgery*. 2013;154:655-660. doi:10.1016/j.surg.2013.04.032