JPPT | Single-Center Retrospective Study

Use of Intrapleural Alteplase in the Treatment of Parapneumonic Effusion in Children: A Report of a 10-year Experience

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OBJECTIVES Intrapleural alteplase is used in children with parapneumonic effusion (PPE) with variable dosing strategies. We compared the outcomes of a lower (≤2 mg) and a higher (>2 mg) alteplase dose in children with PPE.

METHODS A retrospective study was conducted among admitted patients younger than 18 years who received at least 1 intrapleural alteplase dose from July 2014 to May 2023. The primary outcome was the treatment failure rate. Secondary outcomes included chest tube output and duration of placement and hospital and pediatric intensive care unit (PICU) length of stays.

RESULTS Seventy-two patients were included (lower dose: 62.5% vs higher dose: 37.5%) with a median age of 5 years (IQR, 1–8 years). The median alteplase dose was 2 mg (IQR, 2–4 mg). Treatment failure occurred in 10 (14%) patients. The lower dose group had a similar failure rate compared with the higher dose group (lower dose: 9% vs higher dose: 22%; p = 0.161), despite a statistically significant higher median chest tube output in the higher dose group (346 [IQR, 256–466] vs 175 [IQR, 70–358] mL/24h; p = 0.002). However, after adjusting for weight, both groups had a similar output (12 mL/kg/24h). Alteplase instillation after primary video-assisted thoracoscopic surgery (VATS) was associated with a significant reduction in the duration of chest tube placement and hospital and PICU stays.

CONCLUSIONS Lower alteplase doses (≤2 mg) were effective for most children with PPE. Alteplase combined with primary VATS might be associated with better outcomes.

ABBREVIATIONS LOS, length of stay; PICU, pediatric intensive care unit; PPE, parapneumonic effusion; VATS, video-assisted thoracoscopic surgery

KEYWORDS alteplase; chest tube; children; empyema; parapneumonic effusion; VATS

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Introduction

Pneumonia is associated with significant morbidity and mortality worldwide, particularly among children younger than 5 years of age.[1] While patients typically recover with the use of antimicrobials and supportive care, some patients develop complications.[2] While the incidence of parapneumonic effusion (PPE) and empyema in children in the United States has decreased after the introduction of the pneumococcal vaccines,[3] the overall incidence appears to be increasing globally over the past decade.[4–8] Approximately 40% to 50% of children admitted with pneumonia develop a PPE, and many of them require additional therapy, including surgical intervention.[9,10]

Current practice guidelines recommend 2 strategies for the initial management of complicated PPE as follows: chest tube drainage with intrapleural fibrinolytic therapy and video-assisted thoracoscopic surgery (VATS).[11–13] Two systematic reviews of randomized trials demonstrated similar rates of treatment failure and mortality between the 2 strategies.[14,15] However, there were inconsistent findings regarding the differences in hospital length of stay (LOS) and cost.[14–17] An economic analysis found that chest tube drainage with fibrinolytic therapy was the more cost-effective strategy for children with PPE, based on limited outdated data.[16] Furthermore, a recent report that included nearly 3500 children with PPE showed that patients treated with primary VATS had a shorter hospital and pediatric intensive care unit (PICU) LOS and reduced use of health care resources, including radiographic studies and mechanical ventilation, which could reduce overall hospitalization costs.[17]

Older fibrinolytic agents, such as streptokinase and urokinase, were initially evaluated for the treatment of

patients with PPE yielding positive outcomes.[18] However, their use has been replaced by alteplase (tissue plasminogen activator) for safety reasons. Alteplase has been used frequently with variable dosing strategies for children with PPE.[12] The 2011 Pediatric Infectious Diseases Society and the Infectious Diseases Society of America pediatric pneumonia guidelines recommend 2 dosing regimens based on the results of 2 prospective studies: a fixed dose (4 mg) daily for 3 days and a weight-based dose (0.1 mg/kg, maximum 3 mg) every 8 hours for 3 days.[11,19,20] However, observational studies have reported various dosing strategies, ranging from 0.5 to 10 mg, given as a fixed,[21–24] weight-based,[25–27] or ultrasound-grade-based[28,29] regimen, with positive overall outcomes.

Given the variability in alteplase dosing among children with PPE in the available literature, more evidence is needed to help define an optimal dosing regimen. This study reports outcomes associated with a 10-year experience of children treated with intrapleural alteplase for PPE, aiming to evaluate the clinical outcomes of lower alteplase doses (≤2 mg) compared with higher doses (>2 mg).

Materials and Methods

Participants. This study was a single-center, retrospective chart review conducted at an academic children's hospital between July 2014 and May 2023. All children younger than 18 years of age who received at least 1 dose of intrapleural alteplase for the treatment of a thoracic effusion were included. Patients who received alteplase through a peritoneal tube for intra-abdominal infections were excluded. Thoracic effusion was defined as a PPE associated with any etiology.

Treatment. The treatment approach for PPE in children at our institution is not standardized, and each patient is managed differently, primarily based on physician preference. Chest tube placement is the usual first-line strategy with or without fibrinolytic therapy. Alteplase therapy initiation and discontinuation are mostly guided by chest tube output along with clinical assessment. The alteplase dose regimen varies depending on the patient's age and clinical situation; doses used in patients in our analysis ranged from 0.5 to 15 mg.

Surgical evaluation is performed at various intervals. While VATS is usually deferred until the patient is not improving with chest tube drainage and fibrinolytic therapy, some patients are treated initially with VATS, followed by alteplase therapy, which is initiated on postoperative day 1 or 2. This approach is justified as appropriate by the surgery team, as the patient is likely to require surgery eventually due to the severity of the PPE.

Outcomes. The primary outcome for our analysis was the rate of composite treatment failure, defined as a need for VATS following chest tube placement and alteplase therapy and/or the development of recurrence within 6 months of the index dose. The secondary outcomes evaluated were chest tube output, expressed as milliliters per 24 hours and milliliters per kilogram per 24 hours following alteplase administration, duration of chest tube placement, hospital LOS, PICU LOS, and all-cause 6-month mortality. Chest tube output was recorded after each alteplase instillation, and the average output for each patient was used to estimate the median output of the dose group. The duration of chest tube placement, hospital LOS, and PICU LOS were calculated starting from the chest tube insertion date.

Data Collection. A list of patients who received intrapleural alteplase was retrieved using our institution's electronic health record. Data were collected from the patient's electronic health records and included demographic data (age, sex, race, weight, and height); comorbidities; reason for admission; indication for chest tube insertion; dates of chest tube insertion and removal; dates of hospital admission and discharge; dates of PICU admission and discharge; baseline temperature and supplemental oxygen requirements; baseline and after alteplase laboratory results; baseline and after alteplase chest tube output; baseline chest X-ray impression; microbiological culture results; antimicrobials administered; alteplase doses and volumes; thoracic surgeries; and clinical outcomes (treatment failure, recurrence, and mortality). For children younger than 2 years of age, obesity was defined as a weight-for-length percentile above the 95th percentile using the World Health Organization growth charts.[30] For children older than 2 years, obesity was defined as a body mass index above the 95th percentile using the Centers for Disease Control and Prevention body mass index–for-age growth charts.[31]

Statistical Analysis. Formal sample size calculation was not performed, as all eligible patients were included. Descriptive statistical analysis was conducted using Microsoft Excel software, Version 16.81 (Redmond, WA). Proportions (frequencies) were used for categorical variables. Continuous variables were summarized as median (IQR). IBM SPSS Statistics, Version 29.0 (IBM Corp., Armonk, NY) was used for inferential analysis. The difference in treatment failure between the lower (≤2 mg) and the higher (>2 mg) alteplase dose groups was assessed using the χ^2 or Fisher's Exact test. The Mann-Whitney *U* test was used for continuous data. All p values were 2 tailed, and a value of 0.05 or less was considered significant.

Post-hoc analyses for the primary and secondary outcomes were performed for the following 3 groups: (1) patients who received initial therapy with alteplase alone vs those who received alteplase with primary VATS; (2) patients with PPE caused by pneumonia; and (3) children younger than 3 months of age.

Results

Seventy-six patients were screened; 72 were included in the final analysis. Four patients were excluded because they received alteplase for effusions associated with intra-abdominal infections through a peritoneal tube or abdominal drainage device.

Baseline Characteristics. Table 1 summarizes the baseline characteristics of the included patients. The median age was 5 years (IQR, 1–8 years), with a similar proportion of males and females (50% each). All the included patients had variable degrees of PPE secondary to various etiologies, with pneumonia being the most common etiology (75%); 2 patients with pericardial effusion had an associated PPE. Alteplase was administered as intrapleural for all included patients. There were considerable differences between the 2 dose groups. The lower dose group was younger (2.2 [IQR, 0.7–6] years vs 8 [IQR, 5–14] years), had fewer obese patients (18% vs 37%), and had lower supplemental oxygen requirements (40% vs 63%).

Approximately 50% of patients had a positive culture result at some time during their hospitalization. The most common isolate was methicillin-resistant *Staphylococcus aureus* (n = 10). The median duration of antibiotic therapy was 22 days (IQR, 18–26 days). Table 2 summarizes infectious disease characteristics.

Intrapleural Alteplase Therapy. Overall, the median alteplase dose was 2 mg (IQR, 2–4 mg); most patients (n = 19; 26%) received three doses. Most patients received no more than 1 dose per day (n = 51; 71%). A concentration of 1 mg/10 mL was used in most patients (n = 68; 94%). The lower-dose group received a median dose of 2 mg (IQR, 2–2 mg), whereas the higher-dose group received a median dose of 4 mg (IQR, 4–4 mg). The majority received alteplase as initial therapy (69%), defined as treatment given within

Table 1. Baseline Characteristics

Characteristic*	All Patients (*N* = 72)	Alteplase Dose ≤2 mg (n = 45)	Alteplase Dose >2 mg† (n = 27)
Sex, male	36 (50%)	21 (47%)	15 (56%)
Age, yr	5 (1–8)	2.2 (0.7–6)	8 (5–14)
Race/ethnicity			
White	37 (51%)	24 (53%)	13 (48%)
African American	27 (38%)	17 (38%)	10 (37%)
Hispanic	4 (6%)	2 (4%)	2 (7%)
Asian	1 (1%)	1 (2%)	0 (0%)
Others	3 (4%)	1 (2%)	2 (7%)
Previous health issues			
Asthma	8 (11%)	4 (9%)	4 (15%)
Obesity	18 (25%)	8 (18%)	10 (37%)
Hospital LOS before chest tube insertion, days	2 (1–4)	2 (1–5)	1 (0–3)
PICU LOS before chest tube insertion, days	0 (0–2)	1 (0–2)	0 (0–1)
Chest tube output before alteplase			
mL/24 h	55 (16–178)	36 (10–94)	175.2 (67–269)
mL/kg/24 h	3 (1–7)	3 (1–6)	3 (1–7)
Supplemental oxygen requirement	46 (64%)	29 (40%)	17 (63%)
Indication for chest tube			
Parapneumonic effusion	70 (97%)	43 (96%)	27 (100%)
Pneumonia	54 (75%)	33 (73%)	21 (77%)
Chylothorax	6 (8%)	5 (11%)	1 (4%)
Retropharyngeal abscess	2 (3%)	1 (2%)	1 (4%)
Post–thoracic/abdominal surgery	2 (3%)	1 (2%)	1 (4%)
Malignancy/mass	2 (3%)	1 (2%)	1 (4%)
Trauma	2 (3%)	1 (2%)	1 (4%)
Splenic abscess	1 (1%)	0 (0%)	1 (4%)
Pancreatitis	1 (1%)	1 (2%)	0 (0%)
Pericardial effusion	2 (3%)	2 (4%)	0 (0%)

LOS, length of stay; PICU, pediatric intensive care unit

* All values expressed as median (IQR) or count (frequency).
† Patients who received at least one alteplase dose > 2 mg.

Table 2. Infectious Diseases Characteristics

Characteristic	All Patients (*N* = 72)
Positive culture results, n (%)*	37 (51)
Pathogen identification, n (%)†	
Methicillin–resistant *Staphylococcus aureus*	10 (21)
Streptococcus pneumoniae	8 (17)
Methicillin–susceptible *Staphylococcus aureus*	6 (13)
Streptococcus pyogenes	4 (8)
Streptococcus anginosus/constellatus/intermedius	4 (8)
Escherichia coli	2 (4)
Enterobacter cloacae	2 (4)
Other	12 (25)
Antibiotics administered before admission, n (%)	33 (46)
Antibiotics administered during admission, n (%)	68 (94)
Antibiotics administered after discharge, n (%)	50 (69)
Duration of antibiotics, median (IQR), days	
Inpatient antibiotics	10 (8–16)
Discharge antibiotics	13 (10–14)
Total	22 (18–26)

* Number of patients with any culture results identified during hospitalization.
† Pathogen identified from the results of blood, pleural, endotracheal, and pericardial cultures during hospitalization.

the first 2 days after chest tube insertion. Seventeen patients received alteplase with primary VATS, and 2 received intrapleural dornase alfa therapy. The treatment-failure group (n = 10) received a higher median alteplase dose (4 vs 2 mg) compared with the treatment-success group (n = 62). The characteristics of alteplase therapy are outlined in Table 3. Alteplase dose per age and dose per weight per age of alteplase are illustrated in Figure 1.

Treatment Outcomes. Treatment failure occurred in 10 (14%) patients; 7 required VATS and 3 had recurrent PPE. There was no significant difference in treatment failure rate between patients who received an alteplase dose of 2 mg or less compared with those who received a higher dose of more than 2 mg (9% vs 22%; p = 0.161). The median time to rescue VATS was 4 days (IQR, 4–8 days) after chest tube insertion and 3 days (IQR, 3–7 days) after alteplase initiation. The median chest tube output following alteplase instillation was 279 mL/24h (IQR, 120–432 mL/24h). The median duration of chest tube placement was 5 days (IQR, 4–9 days) (Table 4). A higher chest tube output (346 vs 175 mL/24h; p = 0.002) and a longer duration of chest tube placement (8 vs 5 days; p = 0.004) were observed in the higher dose group. However, after adjusting for weight, both groups showed a similar chest tube output (12 mL/kg/24h). There were no significant differences in hospital LOS, PICU LOS, or mortality rate.

Four patients died during the 6-month interval from the first alteplase dose. The causes of death were reported as cardiac arrest secondary to COVID-19 respiratory failure, cor pulmonale, right atrial perforation, and septic shock.

Figure 2 illustrates the differences between the median chest tube output 24 hours before and after the first alteplase dose. There was a higher rate of increment after the first alteplase dose in the lower dose group compared with the higher dose group (378% vs 118%). After adjusting for weight, both groups showed a comparable increment rate (333% vs 329%). Supplemental Table S1 shows treatment outcomes between treatment success and failure groups. Supplemental Table S2 shows laboratory values before and after alteplase therapy.

Post-hoc Analyses. In patients receiving alteplase with primary VATS, a chest tube was inserted immediately following the VATS, and alteplase was initiated in a median of 2 days (IQR, 1–2 days) after the VATS. Patients who received this combined therapy (n = 17) had a lower treatment failure rate (6% vs 17%; p = 0.434) compared with those who received alteplase alone (n = 54); however, this difference was not statistically significant (Table 5). Patients who received alteplase alone had a higher chest tube output (322 vs 166 mL/24h; p = 0.005). This was consistent after adjusting for weight (14 vs 10 mL/kg/24h; p = 0.046). Additionally, combination therapy was associated with a shorter duration of chest tube placement (4 vs 6 days; p = 0.001), hospital LOS (7 vs 13 days; p = 0.001), and PICU LOS (2 vs 11 days; p = 0.01).

In patients with pneumonia (n = 54), there were similar outcomes compared with the total study population (n = 72): treatment failure rate (13% vs 14%); median chest tube output (12 mL/kg/24h both groups); median duration of chest tube placement (5 days both groups); median hospital LOS (9 vs 10 days); and median PICU LOS (6 vs 7 days). Similarly, a higher dose was not associated with better outcomes (Supplemental Table S3).

Eight children younger than 3 months of age (median age, 23 days; range, 10–83 days) were included in a separate analysis (Supplemental Table S4). The indication for chest tube placement in these patients was PPE associated with pneumonia (n = 3), chylothorax (n = 3), pericardial effusion (n = 1), and intra-abdominal surgery (n = 1). All patients were treated with the lower dose strategy and achieved a 100% treatment success rate. The median duration of chest tube placement was 6 days (IQR, 4–11 days); the median hospital LOS was 57 days (IQR, 36–85 days); and the median PICU LOS was 57 days (IQR, 34–85 days).

Table 3. Alteplase Treatment Characteristics

Variable	All Patients (*N* = 72)	Treatment Success (n = 62)	Treatment Failure (n = 10)
Dose, mg			
Median (IQR)	2 (2–4)	2 (2–4)	4 (2–4)
Mean ± SD	2.8 ± 2.0	2.7 ± 2.1	3 ± 1.2
Dose, mg/kg			
Median (IQR)	0.13 (0.08–0.19)	0.12 (0.09–0.18)	0.14 (0.07–0.20)
Mean ± SD	0.15 ± 0.11	0.15 ± 0.12	0.16 ± 0.11
Volume, mL			
Median (IQR)	20 (20–40)	20 (20–40)	40 (20–40)
Mean ± SD	25.3 ± 11.7	24.4 ± 11.5	30.6 ± 11.6
Number of doses, n (%)			
1	18 (25)	16 (26)	2 (20)
2	9 (13)	8 (13)	1 (10)
3	19 (26)	15 (24)	4 (40)
4	12 (17)	12 (19)	0 (0)
> 4	14 (19)	11 (18)	3 (30)
Type of therapy, n (%)			
Initial therapy*	50 (69)	43 (69)	7 (70)
Rescue therapy†	22 (31)	19 (31)	3 (30)
Time to alteplase administration, median (IQR), days	1 (1–3)	2 (1–3)	1 (1–3)
Adjunctive dornase alfa, n (%)	2 (3)	2 (3)	0 (0)
Alteplase with primary VATS, n (%)	17 (24)	16 (22)	1 (10)

VATS, video-assisted thoracoscopic surgery

* Alteplase given within the first 2 days of chest tube placement.

† Alteplase given after 2 days of chest tube placement due to inadequate chest tube output.

Discussion

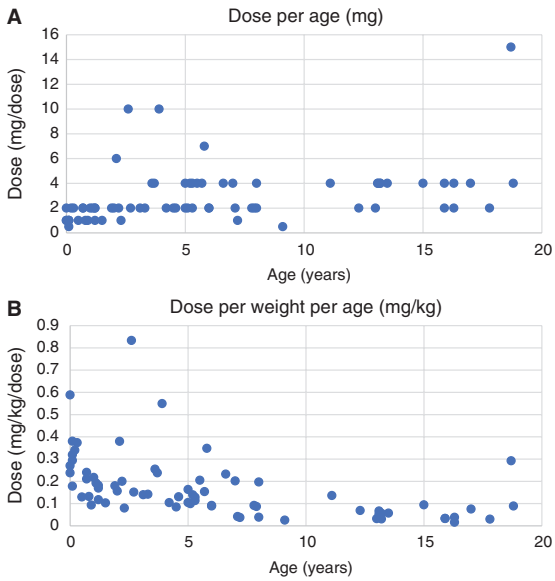
In this retrospective analysis, we report a 10-year experience with intrapleural alteplase for the management of PPE in children (*N* = 72). There was an overall treatment failure rate of 14%, which is comparable to results from previous studies that have reported various rates, including <10%,[17,23,28,29] 10–16.6%,[16,19,26,32,33] and >20%.[22] These studies used various fibrinolytic agents with different dosing strategies, and treatment failure was defined differently across studies. The median hospital LOS after chest tube placement was 10 days, slightly higher than LOS reported in both prospective (median, 6–6.9 days;[19,33] mean, 7.7–9 days[34,35]) and retrospective (median, 6.2–9 days[21,32,36]) studies.

There are 3 key findings from our study. First, lower intrapleural alteplase doses (≤2 mg) were associated with comparable clinical outcomes compared with higher alteplase doses (>2 mg). Our findings may have been influenced by disease severity, which we were unable to assess, and the number of patients who received primary VATS, which was higher in the ≤2 mg group (26.6% vs 18.5%). However, other studies using similar lower doses (1–2 mg) have reported positive overall outcomes.[21,28,29] In a retrospective study of 32 children (mean age, 6.8 years) treated for PPE with intrapleural alteplase, 81% received 1 mg doses, and 19% received 2 mg doses. Treatment success was achieved in 97% of patients.[28]

Our analysis showed that younger children (≤6 years) received a higher weight-based dose (≥0.1 mg/kg) compared with older children (>6 years) (Figure 2B). However, this difference is less likely to affect the outcomes because patients with treatment failure of all ages received a comparable median weight-based dose compared with the treatment-success group (n = 10; 0.14 mg/kg vs n = 62; 0.12 mg/kg).

In this study, most patients (64%) received only 1 to 3 alteplase doses, a finding consistent across both the treatment success (63%) and failure (70%) groups. While 2011 guidelines recommend 3 and 9 doses for the 4 mg fixed and the weight-based dosing regimens, respectively,[11] fewer doses might be sufficient for most patients. Thus, the decision to give repeated alteplase doses should be individualized based on patient response rather than an arbitrary number of doses. Our findings are consistent with those of Baram and colleagues,[23] who reported a 10-year prospective study evaluating outcomes associated with intrapleural

Figure 1. Alteplase dose per weight and age.



(A) The majority of patients aged ≤5 years received alteplase doses ≤2 mg.
(B) Patients aged <6 years received higher milligram per kilogram doses (≥0.1 mg/kg) compared with those aged >6 years (<0.1 mg/kg).

alteplase (0.1 mg/kg) in children with PPE; the mean number of alteplase doses administered was 2.1 doses (range, 1–3 doses). In the 95 patients assessed, the treatment success rate was approximately 98%.[23]

Although administration of fewer total alteplase doses appears to be effective, the optimal frequency of alteplase instillation remains unclear. Published studies have reported frequencies of daily,[19] twice daily,[29] three times daily,[20] and four times daily.[26] A randomized trial demonstrated higher than expected chest tube output the day following twice-daily dosing, suggesting potential benefit compared with once-daily dosing.[27] Another study that evaluated twice-daily dosing showed a significant reduction in the mean days of alteplase therapy from 4.1 to 2.8 days while eliminating the need for surgical intervention, leading to an insignificant reduction in the mean LOS.[29] In our analysis, we did not evaluate the frequency of alteplase instillation due to the lack of a standardized protocol, but most patients received once-daily dosing.

A second important finding is that alteplase therapy following primary VATS as combination therapy for children with PPE might be associated with better outcomes compared with alteplase therapy alone. While previous studies showed similar outcomes between VATS and fibrinolytic therapy when used alone,[14–17] little evidence is available for the combination. Gates and colleagues[21] reported that surgery (with or without fibrinolytic therapy) in children with PPE was associated with a significant increase in hospital and PICU LOS. In contrast, we found that the combination of primary VATS and alteplase was associated with a clinically and statistically significant reduction in the duration of chest tube placement, as well as hospital and PICU LOS, which could result in a reduction in overall cost. Variation between the 2 studies could be related to the fact that we only included primary VATS with alteplase, whereas Gates et al[21] included patients who received VATS at all stages of therapy with or without fibrinolytic therapy. Furthermore, owing to the lack of a control group of patients treated with VATS alone, it is possible that the positive impact was primarily driven by the VATS procedure. However, previous studies suggest that primary VATS and

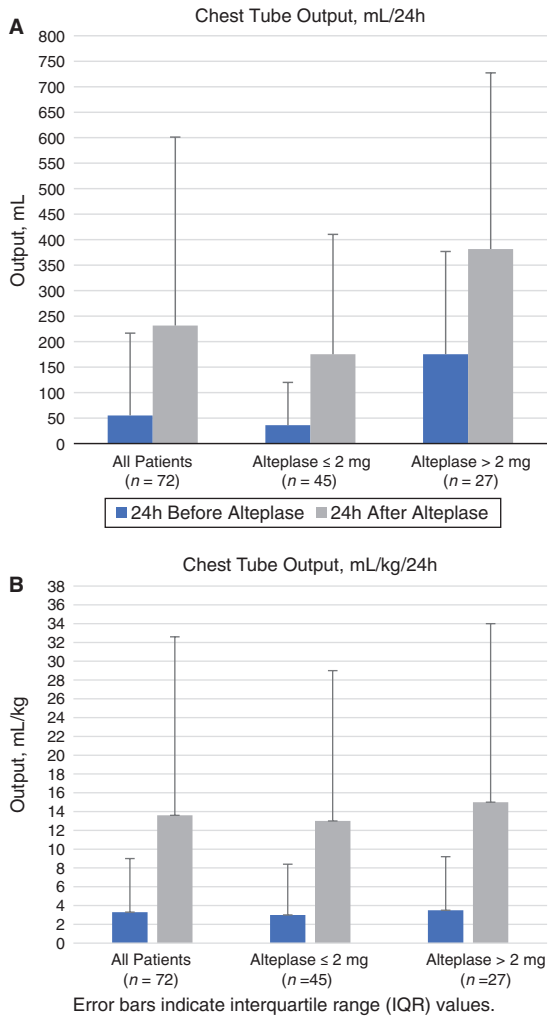
Table 4. Treatment Outcomes According to Alteplase Dose

Outcome*	All Patients (*N* = 72)	Alteplase dose ≤2 mg (n = 45)	Alteplase dose >2 mg† (n = 27)	p value
Primary outcomes				
Treatment failure	10 (14%)	4 (9%)	6 (22%)	0.161
Surgery	7 (10%)	2 (4%)	5 (19%)	–
Recurrence	3 (4%)	2 (4%)	1 (3%)	–
Secondary outcomes				
Chest tube output				
mL/24 h	279 (120–432)	175 (70–358)	346 (256–466)	0.002
mL/kg/24 h	12 (6–23)	12 (6–19)	12 (5–23)	0.949
Duration of chest tube placement, days‡	5 (4–9)	5 (3–7)	8 (4–12)	0.004
Hospital LOS, days	10 (8–26)	9 (7–21)	13 (8–30)	0.321
PICU LOS, days	7 (3–26)	6 (3–21)	14 (6–29)	0.191
6-month all–cause mortality§	4 (6%)	2 (4%)	2 (7%)	–

LOS, length of stay; PICU, pediatric intensive care unit

* All values expressed as median (IQR) or count (frequency).
† Patients who received at least one dose of >2 mg.
‡ Calculated from the first alteplase dose.
§ All patients died before treatment failure could be assessed.

Figure 2. Median chest tube output 24 hours before and after the first alteplase dose by treatment group.



Error bars indicate interquartile range (IQR) values.
(A) For patients in the alteplase dose ≤2 mg group, the median chest tube output increased by 387% from 36 mL per 24 hours before alteplase administration to 175.2 mL per 24 hours after alteplase administration. For the patients in the alteplase dose >2 mg group, the median chest tube output increased by 118% from 175.2 mL per 24 hours before alteplase administration to 381.6 mL per 24 hours after alteplase administration.
(B) For patients in the alteplase dose ≤2 mg group, the median chest tube output increased by 333% from 3 mL/kg/24h before alteplase administration to 13 mL/kg/24h after alteplase administration. For the patients in the alteplase dose >2 mg group, the median chest tube output increased by 329% from 3.5 mL/kg/24h before alteplase administration to 15 mL/kg/24h after alteplase administration.

fibrinolytic therapy alone are associated with similar outcomes.[14–17]

A total of 24 patients underwent VATS at various intervals in our analysis: 17 underwent primary VATS, and 7 underwent rescue VATS after initial alteplase (treatment failure). The timing of therapies and how they differ between the 2 groups might raise a concern. The difference in days between VATS and alteplase initiation was 2 days (IQR, 1–2 days) for the combination group (primary VATS) and 3 days (IQR, 3–7 days) for the treatment failure group (rescue VATS). While this could affect the validity of treatment failure as an outcome, secondary outcomes were better in the combination therapy (Table 5) compared with the treatment failure group (Supplementary Table S1). One possible explanation is that VATS early in the disease course might be associated with better outcomes than VATS performed as rescue therapy. A recent retrospective study conducted by Di Mitri et al[37] found that early VATS performed within 5 days from admission was associated with a shorter duration of PICU and hospital LOS compared with VATS performed later in the hospital admission. The PICU and hospital LOS were numerically lower in our patients who received combination therapy compared with the early VATS therapy reported by Di Mitri et al[37] (2 vs 7 days for PICU LOS; 7 vs 22 days for hospital LOS). Additional studies are needed to confirm whether the improved outcomes in our study were related to the timing of VATS or the use of combination therapy.

Table 5. Treatment Outcomes According to Initial Therapy

Outcome*	Alteplase (n = 55)	Alteplase + Primary VATS (n = 17)	p value
Primary outcomes			
Treatment failure	9 (17)	1 (6)	0.434
Secondary outcomes			
Chest tube output			
mL/24h	322 (167–450)	166 (67–250)	0.005
mL/kg/24h	14 (6–24)	10 (5–13)	0.046
Duration of chest tube placement, days†	6 (4–11)	4 (3–4)	<0.001
Hospital LOS, days	13 (8–34)	7 (7–8)	<0.001
PICU LOS, days	11 (4–30)	2 (1–7)	0.01
6-month all-cause mortality‡	4 (7)	0 (0)	–

LOS, length of stay; PICU, pediatric intensive care unit; VATS, video-assisted thoracoscopic surgery

* All values are expressed as median (IQR) or count (frequency).
† Calculated from the first alteplase dose.
‡ All patients died before treatment failure could be assessed.

A third key finding is that intrapleural alteplase appears to be effective among children younger than 3 months of age with various thoracic effusions. A recent review suggested that the youngest patient reported in the literature to receive intrapleural alteplase was 3 months.[38] Our study included 8 children younger than 3 months of age (median age, 23 days; range, 10–83 days) who were treated with alteplase doses ranging from 0.5 to 2 mg, achieving a 100% treatment success rate. The median duration of chest tube placement was similar to that of the total population (6 vs 5 days), but the hospital and PICU LOS were higher in this group, likely due to their underlying conditions.

Chest tube output is one of the parameters used to evaluate the effectiveness of alteplase therapy in children with PPE.[12,13] Despite the lack of evidence to guide therapy based on drainage volume in children and its uncertainty as a surrogate marker for treatment success,[12] it has generally been used as the sole primary outcome.[26,27] In our analysis, chest tube output did not correlate with clinical outcomes. Similarly, in a retrospective study evaluating alteplase compared with urokinase in children with PPE, the significantly higher chest tube output seen after alteplase instillation did not translate to superior clinical outcomes compared with the urokinase group.[36] In another prospective study, a significantly shorter hospital LOS was achieved in the fibrinolysis group despite a lower total drainage volume compared with patients who did not receive fibrinolytic therapy.[35]

Limitations of Study

This study has several limitations. First, given the retrospective design, we were unable to assess several crucial factors, including disease severity, all adverse events, and the need for additional procedures (e.g., thoracentesis, additional chest tube insertions). Second, our study included a relatively small sample size, which led to considerable baseline differences between the dosing groups that may have affected the findings. Third, our analysis included patients with thoracic effusions caused by various etiologies, whereas most previous studies included only pneumonia-related etiologies. However, most patients had pneumonia as their primary etiology for PPE, and post-hoc analysis showed similar outcomes when the analysis was restricted to patients with pneumonia. This is one of the few studies describing the use of intrapleural alteplase in children with PPE secondary to the other noninfectious etiologies. Finally, owing to the lack of a standardized protocol, the optimal timing of alteplase instillation following primary VATS (n = 17) cannot be determined; however, most patients received alteplase on postoperative day 1 or 2. Similarly, because treatment failure was defined differently among providers, defining a specific time to treatment failure was challenging (rescue VATS; n = 7). Different practice guidelines recommend different timing for surgical evaluation (2–3 vs 7 days after initial therapy). Therefore, in all our patients who were initially treated with chest tube placement and alteplase, the need for VATS at any time was considered a treatment failure.

There are several opportunities for future research to improve outcomes in children with PPE. Additional prospective studies are needed to determine the optimal alteplase dosing strategy and to evaluate the cost-effectiveness of various treatment approaches. Although, randomized trials may not be feasible for various reasons, the design and implementation of institutional protocols and pathways can significantly contribute to the literature.[29] Although predictors of treatment failure have been evaluated previously in children with PPE,[22,35] additional studies are needed to identify populations at risk that could potentially benefit from primary VATS with alteplase to improve clinical and economic outcomes. While several studies have reported the effectiveness of alteplase therapy at various doses, future research should focus on safety parameters. Even with the use of relatively low alteplase doses, bleeding has been reported.[39] Additionally, weight-based dosing should be further investigated in various age groups. Only 2 weight-based alteplase doses have been evaluated in children with PPE. The current standard dose of 0.1 mg/kg has been evaluated in several studies;[20,25,27] however, studies use different maximum alteplase doses. A larger alteplase dose of 0.4 mg/kg extrapolated from adult data was evaluated in 1 study.[26] Of note, none of the aforementioned studies evaluated weight-based dosing across different age groups. Prolonged dwell time after alteplase instillation has been reported to reduce the required dose in adults,[40,41] but this has not been evaluated in children. Last, in clinical practice, many providers use fibrinolytic therapy only when there is inadequate chest tube output. In our study, only 31% of patients received alteplase as a rescue therapy. Currently, it is unclear whether the timing of alteplase administration affects outcomes, as previous studies have shown conflicting results.[21,27,42]

Conclusions

Lower alteplase doses (≤2 mg) resulted in successful treatment of PPE in most patients, including patients younger than 3 months. Higher alteplase doses were not associated with better clinical outcomes. While intrapleural fibrinolytic therapy alone appears to be effective in resolving PPE, alteplase combined with primary VATS may be associated with better clinical and economic outcomes in some patients. Larger studies are required to confirm these results and estimate the cost-effectiveness of various treatment strategies.

Article Information

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