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Clinical Investigation

Retrospective Analysis of Large-Dose Intrapleural Alteplase for Complicated Pediatric Parapneumonic Effusion and Empyema

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OBJECTIVES: Medical treatment of complicated parapneumonic effusion or empyema in pediatric patients includes antibiotics and pleural space drainage. Intrapleural fibrinolysis may facilitate pleural drainage; however, there is a lack of consensus regarding the optimal dosing regimen. The primary purpose of this study was to evaluate the efficacy and safety of a large-dose intrapleural alteplase regimen in pediatric patients. Secondarily, this investigation sought to differentiate the clinical characteristics of responders and non-responders to intrapleural alteplase therapy.

METHODS: All patients with parapneumonic effusions treated with intrapleural alteplase between June 2003 and December 2011 were reviewed retrospectively. Efficacy was assessed by comparing chest tube output, in mL/hr and mL/kg/hr, for 24 hours before and after the first dose of alteplase. Additional efficacy outcomes included duration of *in situ* chest tubes, a need for surgical intervention for pleural effusion, and length of hospital stay. Safety was assessed by frequency and severity of adverse events. Non-responders and responders were compared based on demographic and disease characteristics. Responders were defined as patients who did not require surgical intervention after intrapleural alteplase therapy.

RESULTS: Seventy-three patients, aged 0.5 to 22.5 years, received intrapleural alteplase to facilitate pleural drainage. Median alteplase dose was 7 mg (range, 3 to 10 mg; median 0.38 mg/kg). Chest tube output increased from 10.7 to 24.2 mL/hr ($p = 0.006$), and median length of hospital stay was 9 days. Eighty-four percent of patients were responders. The most common adverse events were pain (20.5%) and oxygen desaturation greater than 10% from baseline (16.4%). High-flow nasal cannula was the most common intervention for oxygen desaturation to 80% to 90%. Nine patients (12%) required a blood transfusion during the study.

CONCLUSION: Large-dose intrapleural alteplase is effective in facilitating pleural drainage in pediatric patients with complicated parapneumonic effusion or empyema. Common adverse effects include pain and oxygen desaturation. The potential for bleeding warrants clinical monitoring.

INDEX TERMS: empyema, pediatrics, pleural effusion, pneumonia, tissue plasminogen activator

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INTRODUCTION

Pneumonia is the leading cause of death in children worldwide.[1] It is also the most common cause of hospitalization of children in the United States.[2] Local complications (i.e., empyema, lung abscess, necrotizing pneumonia, bronchopleural fistula) in pediatric patients with pneumonia, more than 97% of which are caused by empyema, increased by 78% from 1997 to 2006.[3] The bacterial etiology of complicated parapneumonic effusion or empyema has fluctuated over the years with the introduction of various vaccines, but the most common causative bacteria are *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. Epidemiological studies have shown that the incidence of *S aureus* empyema has increased over time.[4,5] While the incidence of *S pneumoniae* empyema since the introduction of the pneumococcal conjugate vaccine has varied in regional reporting, the overall incidence in the United States remains unchanged despite a 45% decrease in the incidence of pneumococcal pneumonia from 1997 to 2006.[6-8]

Medical treatment of complicated parapneumonic effusion or empyema in pediatric patients

consists of appropriate antibiotics and drainage of the pleural space. However, much debate exists concerning the preferred treatment for pediatric parapneumonic effusion that fails antibiotics with or without drainage of the effusion. Options for the management of these situations include tube thoracostomy plus fibrinolytics, video-assisted thoracoscopic surgery (VATS), and open thoracotomy.[9-14] Published guidelines recognize tube thoracostomy with fibrinolytics and VATS as having similar outcomes for treatment of complicated parapneumonic effusion or empyema. Tube thoracostomy with fibrinolytics is noted to be a reasonable first-line option in published guidelines.[9,11-13] Most often, the decision regarding which approach to use is left to clinical judgment and institutional practice.

Intrapleural fibrinolysis facilitates pleural drainage by lysing the fibrinous strands that form in more advanced stages of complicated parapneumonic effusion or empyema. This treatment option is less invasive and costly compared to VATS or open thoracotomy.[15-17] Intrapleural streptokinase, urokinase, and alteplase are the fibrinolytics described most often in the literature for the treatment of complicated parapneumonic effusion or empyema.[18-37] In addition, one study reported on the use of reteplase.[38]

Streptokinase use has decreased in lieu of newer agents due to its antigenicity.[39] In 1999, the manufacture of urokinase was halted because the product cell line was found to be contaminated. Urokinase was reapproved by the Food and Drug Administration in 2002 but is not currently available in the United States.[40] Because of the antigenicity of streptokinase and the lack of availability of urokinase in the United States, interest in and use of alteplase has increased significantly.

The use of intrapleural alteplase suffers from the absence of a controlled dosing study or consensus regarding a dosing regimen. Case reports have described the use of fixed doses of 2 to 5 mg of intrapleural alteplase for complicated parapneumonic effusion or empyema in children.[33,34,37] Other retrospective reviews have used fixed doses of 2 to 4 mg and 0.1 mg/kg/dose (maximum 3 mg/dose or 6 mg/dose).[16,32,35,36] The only published prospective trial of alteplase in pediatrics used a fixed 4-mg dose.[15] A recent review article proposed a weight-based dosing regimen of 0.1 to 0.2 mg/kg/dose, diluted to 0.1 mg/mL every 24 hours for 3 doses.[41]

The primary purpose of this study was to evaluate the efficacy and safety of a large-dose intrapleural alteplase protocol for complicated parapneumonic effusion or empyema in pediatric patients. Secondarily, this investigation sought to differentiate the clinical characteristics of pediatric patients who respond to intrapleural alteplase therapy from those of non-responders.

METHODS

This study was a multicenter, retrospective medical record review completed by sequential sampling. The study was conducted at Children's Hospitals and Clinics of Minnesota, a tertiary care hospital system with 2 campuses located in St Paul and Minneapolis, Minnesota. Medical records were reviewed between June 1, 2003, and December 31, 2011. Patients were included in the study if they had a diagnosis, documented in the medical record, of parapneumonic effusion or empyema that was secondary to pneumonia that was treated with intrapleural alteplase (Activase, Genentech Inc, San Francisco, CA). A radiologist's interpretation of imaging studies was used to determine whether an effusion was complex (positive for loculations or septations) or if pulmonary necrosis or an abscess was present.

Patients with non-bacterial pulmonary effusion (e.g., due to trauma or malignancy) were excluded from the study. Patients with multiple admissions during the study period were included only once. The first chest tube to receive alteplase was used to analyze any patients with more than one chest tube who received more than one course of alteplase during the same admission. This study was approved by the Children's Hospitals and Clinics of Minnesota institutional review board.

Patients received intrapleural alteplase (hereafter referred to as alteplase) treatment via a protocol. The protocol dose was 0.4 mg/kg/dose (maximum 10 mg) and diluted in normal saline to 0.2 mg/mL, unless otherwise specified by the ordering physician. All doses were prepared in the pharmacy under aseptic, laminar flow conditions. Dosing frequency was not described by the protocol and was left to physician discretion. Doses were administered by a physician, medical resident, or nurse with a physician's order at the patient's bedside. After administration, the chest tube was clamped for 80 minutes, during

which the patient was rotated every 15 minutes, as his or her condition allowed, into various positions: 1) supine, head, and thorax up 45 degrees, recumbent; 2) supine, head and thorax up 45 degrees, first on the right side and then on the left side; 3) prone, flat; 4) prone, flat, first on the right side, then on the left side; and then 5) prone Trendelenburg, first on the right side, then on the left side. Physician discretion determined when to initiate and discontinue alteplase therapy.

The primary efficacy outcome of the study was the rate of chest tube output in mL/hr and mL/kg/hr. Secondary efficacy outcomes included the number of responders, defined as the number of patients who did not require surgical intervention after alteplase; chest tube duration; and length of hospital stay. Adverse events were recorded as the primary measure of safety and were defined as anaphylaxis, pain, oxygen desaturation greater than 10% from baseline, and any local or systemic bleeding. Lowest hemoglobin (Hgb) concentration and the number of blood transfusions were used as secondary safety outcomes. Demographic and clinical data were used to identify differences between patients who responded to alteplase therapy and those who did not respond. These data included hospital campus, in-patient unit, sex, age, weight, race, presence of complex effusions, presence of necrosis, need for cardiotonic infusions, chest tube type and size, number and duration of chest tubes, alteplase dose and dilution, alteplase dosing interval and number of doses, duration of chest tubes *in situ* prior to alteplase initiation, and baseline laboratory values.

Chest tube output was documented every 24 hours beginning 24 hours prior to the first dose or from the time of chest tube insertion if placement was less than 24 hours prior to administration of the first dose. The volume of alteplase administered was subtracted from the chest tube output data.

Descriptive statistics, including medians and ranges for continuous variables such as patient age and chest tube output rate and frequency distributions for binary and dichotomous variables, such as patient sex, were used to describe patient characteristics and clinical outcomes. The median was used as the measure of central tendency, as the data were not normally distributed. The nonparametric Wilcoxon signed ranks test was used to compare the median chest tube output rate before and after alteplase administration. The Mann-Whitney test was used to compare continuous variables, including chest tube duration and chest tube size, between alteplase responders and non-responders. The chi-square test or Fisher's exact test was used to compare the categorical data between responders and non-responders. A two-sided p value < 0.05 was used as the threshold for significance. Statistical analyses were conducted with SPSS v 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Seventy-three alteplase encounters meeting the inclusion criteria were identified that took place between June 1, 2003, and December 31, 2011. Patient demographics and baseline clinical characteristics are listed in Table 1. One patient received continuous renal replacement therapy and another patient received peritoneal dialysis, continuous renal replacement therapy, and plasmapheresis during hospitalization. Median length of hostpital stay was 9 days (range 4 to 39 days).

Table 2 provides pleural and blood culture results. Sixty-nine bacterial cultures of pleural fluid were performed. Four chest tubes were placed without subsequent culturing of the pleural fluid. Of the 69 patients with pleural cultures, 40 (58%) had negative pleural cultures and 29 (42%) were positive for bacterial growth. During hospitalization, 71 patients had blood cultures drawn and 2 did not. Of these 71 patients, 57 (80%) had a negative blood culture and 14 (20%) had a positive blood culture. Three patients had both a positive blood culture and a positive pleural fluid culture for *S pneumoniae.*

Chest tube sizes varied from 8.5-French (Fr) pigtail catheters to 24-Fr catheters. The 3 most common sizes, each accounting for more than 15% of chest tubes, were 12 Fr, 14 Fr, and 16 Fr. Most often patients required placement of 1 (70%) or 2 (23%) chest tubes, but 1 patient had 5 different chest tubes placed throughout hospitalization. Cumulative duration of chest tubes was a median of 7 days (range, 4 to 21 days). There were 50 instances in which the first dose of alteplase was administered within 24 hours of chest tube placement. For these patients, chest tubes were in place for a median of 12 hours (range, 1 to 24 hours) prior to the first alteplase dose. For the 23

Table 1. Patient Demographic and Baseline Clinical Characteristics (n = 73)

Age (mo)*	50 (6-270)
Male sex†	37 (51%)
Race/ethnicity†	
American Indian	1 (1%)
African American	6 (8%)
Asian	8 (11%)
White	43 (59%)
Hispanic/Latino	5 (7%)
Other	1 (1%)
Not stated	9 (12%)
Weight (kg)*	18.6 (8-79)
Patient care unit while receiving alteplase†	
Medical/surgical unit	37 (51%)
Pediatric intensive care unit	32 (44%)
Both	4 (6%)
Complex effusion†	36 (49%)
Necrosis†	26 (36%)
Patients with cardiotonic infusions†	7 (10%)
Admit laboratory values*	
Hgb (g/dL), n = 72	11.1 (6.6-14.7)
WBC (k/μL), n = 72	14.8 (0.6-41.9)
Temperature (°C), n = 73	37.8 (36.0-41.0)
CRP (mg/dL), n = 71	22 (4-25)

CRP, C-reactive protein; Hgb, hemoglobin; WBC, white blood cell
* median (range)
† n (%)

chest tubes that were placed 24 hours or more prior to the first dose of alteplase, chest tubes were placed for a median of 2 days (range, 1 to 8 days) prior to the first dose.

Characteristics of alteplase therapy are listed in Table 3. Chest tube output increased significantly after the administration of the first dose of alteplase (Figure 1). The difference between chest tube output 24 hours before and after the initial alteplase dose remained statistically significant when the rate was calculated as mL/kg/hr (Figure 2).

Eighteen (25%) patients required surgery for pleural drainage: 12 underwent VATS and 6 underwent open thoracotomy. Of these 18 patients, 11 (61%) had surgery after completion of alteplase therapy, 6 (33%) received alteplase therapy after surgery, and 1 received surgical interventions both before and after alteplase therapy. Overall, 61 of 73 (84%) patients did not receive surgical intervention after alteplase therapy. Statistical significance was maintained for the comparison of chest tube output 24 hours before and after the initial alteplase dose when patients who received alteplase after surgical intervention for pleural drainage were excluded.

Comparison of alteplase responders (n = 61) with non-responders (n = 12) did not reveal any predictors of positive alteplase response. However, 4 significant differences were found between the groups. Responders had a shorter duration of *in situ* chest tubes (6 days vs. 10 days; $p = 0.012$), fewer chest tube insertions (82% vs. 8% with 1 chest tube insertion; $p < 0.001$), smaller chest tubes (58% vs. 25% with a chest tube 14 Fr or smaller; $p = 0.04$), and fewer packed red blood cell transfusions during alteplase therapy (0 patients vs. 2; $p = 0.026$) when compared to non-responders. When the number of transfusions was expanded to include transfusions that occurred within 24 hours after the last dose of alteplase, statistical significance was not retained for responders versus non-responders (7 patients vs. 2 patients; $p = 0.63$).

Twenty-eight patients (38%) experienced an adverse event associated with alteplase administration. The most common adverse events were pain (n = 15; 21%) and oxygen desaturation greater than 10% from baseline (n = 12; 16%). The most common intervention for pain was opioid analgesic administration. High-flow nasal cannula was the most common intervention for patients with an oxygen saturation of 80% to 90%. One patient had oxygen saturations ranging between 70% and 90% which responded to high-flow nasal cannula and another patient had a desaturation event during turning with oxygen saturations ranging between 30% and 40%, which responded to increased oxygen and bag-mask ventilation.

No patients experienced hypersensitivity or allergic reactions. Six patients experienced bleeding: 2 had pulmonary hemorrhage, 2 had a small amount of superficial bleeding at the chest tube insertion site, 1 had an acute output of 400 mL of bloody fluid from the chest, and 1 had a large number of blood clots in the chest tube drainage. Nine patients were transfused with blood during alteplase administration or within 24 hours

Table 2. Positive Culture Results

	Frequency	Percent
Positive pleural fluid cultures (n=29)		
*S pneumoniae**	8	28
S pyogenes	8	28
Alpha-hemolytic *Streptococcus viridans*†	4	14
Methicillin-sensitive *S aureus*	3	10
Methicillin-resistant *S aureus*	3	10
Coagulase-negative *Staphylococcus**	2	7
Bacteroides vulgatus and *Peptostreptococcus micros*†	1	3
Gamma-hemolytic *Streptococcus*, not group D	1	3
Beta-hemolytic *Streptococcus*, group F	1	3
Positive blood cultures (n=14)		
S pneumoniae	11	79
S pyogenes	2	14
Pseudomonas aeruginosa	1	7

* One patient had 2 bacteria present in the pleural culture (*S pneumoniae* and coagulase-negative *Staphylococcus*)
† One patient had 3 bacteria present in the pleural cultures (alpha-hemolytic *Streptococcus*, *Bacteroides vulgatus*, and *Peptostreptococcus micros*)

after the last dose. The median Hgb concentration nadir observed among all patients during alteplase administration or within 24 hours after the last dose was 9.5 g/dL (range, 6.3 to 14.5 g/dL). The median decrease in Hgb concentration from admission to nadir, during or within 24 hours after the last dose of alteplase, was 1.5 g/dL (range, 0 to 5.9 g/dL).

DISCUSSION

Chest tube output increased significantly after alteplase administration in this pediatric population with complicated parapneumonic effusion or empyema. While a statistically significant increase in chest tube output post intrapleural fibrinolytic therapy was noted in other studies, this is the first study to use 0.4 mg/kg/dose (maximum 10 mg). This protocol was created in collaboration between providers and pharmacists in 2002. At the time, there were scarce data in the literature regarding alteplase usage in the pediatric population, and no recommendations were available for a dosing regimen. This dosing regimen was extrapolated from available adult data.

A variety of pediatric dosing regimens are reported in the literature. This is the first report to use an alteplase dosing protocol of 0.4 mg/kg/dose diluted to 0.2 mg/mL in normal saline. Most studies and case reports, including the only prospective trial on this subject, describe a fixed dosing regimen of alteplase. These regimens range from 2 to 5 mg/dose diluted in 20 to 250 mL of normal saline given every 8 to 24 hours. Based on the weights reported in these articles, patients received 0.1 to 0.5 mg/kg/dose of alteplase.[15,16,33-35,37] Only 2 retrospective studies have described a mg/kg alteplase dosing regimen. These 2 studies used a regimen of 0.1 mg/kg/dose (maximum of 3 mg, or 6 mg per dose) in 10 to 100 mL of normal saline given every 8 to 24 hours.[32,36] The protocol in the current study called for an 80-minute alteplase dwell time with positional changes. This is similar to the alteplase dwell time most commonly reported (1 hour), but most reports do not reference how the patient is positioned after dosing.[15,16,32,35-37] One report described alteplase dwell times of 4 to 6 hours, with patient position changes after dose administration.[33,34] In the current study, patients received 1 to 20 doses of alteplase, which is more than what has been described in case reports and retrospective series (1 to 15 doses).[16,32-37] A 3-dose alteplase regimen is the only regimen that has been validated by a randomized, prospective trial.[15]

Most published guidelines recognize alteplase as an option for the treatment of complicated pediatric parapneumonic effusion or empyema but do not offer a recommended alteplase dosing regimen.[9-12] Two regimens were recently recommended for use in review articles. One recommended a fixed regimen of 4 mg in 40 mL of normal saline every 24 hours for 3 doses. This is the only regimen validated by a randomized,

Table 3. Alteplase Dosing Regimen

Alteplase dose, median (range), mg	7 (3-10)
Patients with 0.4 mg/kg dose, n (%)	69 (95%)
Patients with doses truncated at 10 mg, n (%)	24 (33%)
Patients with 0.2 mg/mL dilution, n (%)	68 (93%)
Patients following protocol, n (%)*	66 (90%)
Dosing interval, n (%)	
6 hrs	19 (26%)
8 hrs	45 (63%)
12 hrs	6 (8%)
24 hrs	2 (3%)
Number of doses, median (range)†	4 (1-20)

* Nine patients received alteplase outside of the protocol. Five of these received a different dose of alteplase (three patients received 0.2 mg/kg, one patient received 0.5 mg/kg and one patient received 0.6 mg/kg) and four patients received different dilutions of alteplase (three patients received 0.1 mg/mL and one patient received 1 mg/mL)

† Seven patients received >10 doses, 38 patients received 4-10 doses and 28 patients received ≤3 doses

prospective trial.[13] The other used 3 alteplase doses, 24 hours apart, with a 1-hour dwell time. The authors suggested that alteplase be dosed as follows: for patients 5 to 10 kg, give 1 mg of alteplase in 10 mL of normal saline; for patients 10 to 20 kg, give 2 mg of alteplase in 20 mL of normal saline; for patients between 20 and 30 kg, give 3 mg of alteplase in 30 mL of normal saline; and for patients greater than 30 kg, give 4 mg of alteplase in 40 mL of normal saline.[41]

Despite the wide variety of alteplase dosing regimens, the efficacy findings of this study are consistent with what has previously been reported. Some of the most common measures used to determine alteplase efficacy are length of hospital stay, chest tube output, chest tube duration, and need for surgical intervention. This study found a median length of total hospital stay of 9 days, which is comparable to the average and median total hospital length of stays (8.4 to 10 days) reported in other retrospective studies.[16,32,36] With respect to chest tube output, this study found a significant difference between chest tube output 24 hours before and 24 hours after alteplase administration (10.7 mL/hr vs. 24.2 mL/hr; $p = 0.006$). Similarly, chest tube output 6 hours pre- and 6 hours post-alteplase in a retrospective case series was 3.8 mL/hr and 23.6 mL/hr, respectively ($p < 0.0001$).[34] Other studies have also noted considerable chest tube output post-alteplase dosing.[33,35-37] Median chest tube duration in this study was 7 days, which falls within the higher range of durations reported in the literature (3.5 to 8.7 days).[32,35,36] Alteplase success rates in the literature range from 83% to 100%, with 3 studies noting an 83% success rate.[15,16,32,34-37] These published success rates are similar to the 84% alteplase success rate found in this study.

When comparing the efficacy of intrapleural fibrinolysis to VATS, different studies have suggested the equivalence of and the superiority of each treatment option for the treatment of complicated pediatric parapneumonic effusion or empyema. One prospective study that compared alteplase (4 mg in 40 mL of normal saline) and VATS in children found no significant differences in the length of post-therapy hospitalization, number of post-therapy days with oxygen support, time to defervescence after therapy, or number of analgesic medication doses. However, patients who received a VATS procedure had higher hospital charges ($11,700 vs. $7,600 USD; $p = 0.02$).[15] A second study comparing alteplase to operative therapy (thoracotomy and VATS) in the pediatric population found that patients who were treated with intrapleural fibrinolysis had fewer intensive care unit days, fewer hospital days, and lower total hospital charges.[16] Similar findings have been reported with urokinase as the fibrinolytic agent.[17] Other studies suggest the clinical superiority of VATS to intrapleural fibrinolysis.[26,38,42]

The literature lacks a consensus on the preferred treatment for complicated parapneumonic effusion and empyema. Both intrapleural fibrinolysis and VATS procedures have been shown to be efficacious. Consistent data do not suggest the superiority of one treatment modality with regard to shorter length of hospital stay or clini-

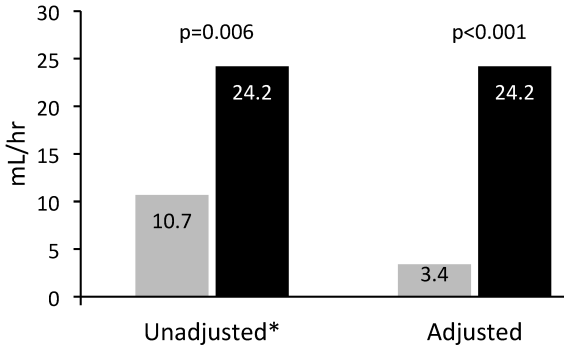

Figure 1. Chest tube drainage after first dose of alteplase (mL/hr).
* Unadjusted data include the initial volume of fluid that immediately flowed out of the pleural space, during chest tube placement for chest tubes inserted within 24 hours of alteplase administration. The adjusted data exclude that volume.
□ = 24 hours pre-alteplase; ■ = 24 hours post-alteplase.

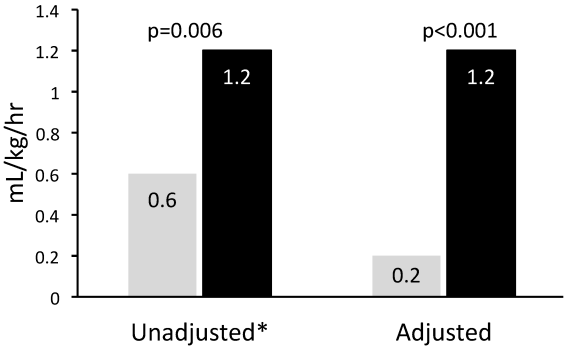

Figure 2. Chest tube drainage after first dose of alteplase (mL/kg/hr).
* Unadjusted data include the initial volume of fluid that immediately flowed out of the pleural space, during chest tube placement for chest tubes inserted within 24 hours of alteplase administration. The adjusted data exclude that volume.
□ = 24 hours pre-alteplase; ■ = 24 hours post-alteplase.

cal outcomes. Furthermore, there are insufficient data to suggest that one fibrinolytic is more efficacious than another. Alteplase is the most commonly used fibrinolytic agent, but no consensus exists regarding its dosing in pediatrics. Whereas one study suggested that patients treated with VATS incur fewer total hospital charges, other studies have shown that patients treated with intrapleural fibrinolysis incur fewer hospital charges.[15-17,42]

The most common adverse events reported in the current study were pain and oxygen desaturation greater than 10% from baseline. These events are consistent with chest tube insertion and fluid instillation into the infected pleural space, both of which are painful. Also, patients with a primary respiratory illness are more likely to display disturbances in oxygen saturation. In this study, oxygen desaturation was most often minor and corrected with high-flow nasal cannula. However, one patient experienced a severe oxygen desaturation event requiring oxygen and bag-mask ventilation. Only one published study has described respiratory adverse events. A retrospective review noted "coughing and mild respiratory distress" in 4 patients.[36] Pain is the adverse event most commonly mentioned in the literature. One review noted mild pain and discomfort in 4 patients and severe pain in 1 patient.[36] A prospective trial found no significant difference in the number of analgesic doses administered to patients who received alteplase or VATS.[15]

No life-threatening adverse events or hypersensitivity reactions were noted in this study. Reports of bleeding were relatively minor. The 2 cases of pulmonary hemorrhage were thought to be related to the necrotic pulmonary process itself rather than the administration of alteplase, although exacerbation of the condition cannot be ruled out. Both patients with pulmonary hemorrhage recovered fully. The patient with abrupt output of bloody fluid and the patient with blood clots in the chest tube fluid each had 1 dose of alteplase held. Dosing then continued without further bleeding. Nine patients (12%) required blood transfusions during the study. This is similar to historical experience at the authors' institution in patients who were treated with a chest tube alone for parapneumonic effusion, suggesting that the transfusions could have been required for reasons other than alteplase administration. The median decrease in Hgb concentration from admission to nadir during or within 24 hours after alteplase observed in this study, 1.5 g/dL, is comparable to the 2.5 g/dL Hgb decrease observed in another retrospective study.[32] Two studies reported minor bleeding in drained pleural fluid with no significant drop in Hgb concentration.[34,36] One case report exists in the literature of a pediatric patient who developed an intrapleural hemorrhage after alteplase administration. Alteplase was discontinued; the patient received a blood transfusion and recovered fully.[43]

Limitations of this study are its retrospective design and consequential lack of control of several factors, such as a standardized diagnosis of complicated parapneumonic effusion or empyema, time to alteplase administration, dosing

interval, and timing of surgical procedures. Another drawback of the study is the subjective nature of the characterization and documentation of adverse events. Adverse events were documented primarily in physician and nursing narrative notes.

CONCLUSION

This study found that a large-dose alteplase regimen effectively facilitated pleural drainage in pediatric patients with complicated parapneumonic effusion or empyema. This regimen appears to be relatively safe, but the potential for bleeding warrants clinical monitoring. A prospective trial comparing low-dose versus large-dose alteplase would be useful to better understand the optimal dose of this approach.

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Abbreviations CRP, C-reactive protein; Fr, French; Hgb, hemoglobin; VATS, video-assisted thoracoscopic surgery; WBC, white blood cell

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