Effectiveness of Intrapleural Tissue Plasminogen Activator and Dornase Alfa vs Tissue Plasminogen Activator Alone in Children With Pleural Empyema
A Randomized Clinical Trial

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IMPORTANCE Clinical guidelines recommend that children with pleural empyema be treated with chest tube insertion and intrapleural fibrinolytics. The addition of dornase alfa (DNase) has been reported to improve outcomes in adults but remains unproven in children.

OBJECTIVE To determine if intrapleural tissue plasminogen activator (tPA) and DNase is more effective than tPA and placebo at reducing hospital length of stay in children with pleural empyema.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, parallel-group, placebo-controlled, superiority randomized clinical trial included children diagnosed as having pleural empyema requiring drainage aged 6 months to 18 years treated at 6 tertiary Canadian children’s hospitals. A total of 379 children were assessed for eligibility; 281 were excluded and 98 were randomized. One child was excluded after randomization for not meeting the inclusion criteria. Data were collected from March 4, 2013, to December 13, 2017.

INTERVENTIONS Participants underwent chest tube insertion and 3 daily administrations of intrapleural tPA, 4 mg, followed by DNase, 5 mg (intervention group), or 5 mL of normal saline (placebo; control group). Participants, families, clinical staff, and members of the study team were blinded to allocation.

MAIN OUTCOMES AND MEASURES The primary outcome was hospital length of stay from chest tube insertion to discharge. Secondary outcomes included time to meeting discharge criteria, time to chest tube removal, mean fever duration, additional pleural drainage procedures, hospital readmissions, and total health care cost.

RESULTS Of the 97 analyzed children with pleural empyema, 52 (54%) were male, and the mean (SD) age was 5.1 (3.6) years. A total of 49 children were randomized to tPA and DNase and 48 were randomized to tPA and placebo. Treatment with tPA and DNase was not associated with decreased hospital length of stay compared with tPA and placebo (mean [SD] length of stay, 9.0 [4.9] vs 9.1 [5.3] days; mean difference, −0.1 days; 95% CI, −2.0 to 2.1; P = .96). Similarly, no significant differences were observed for any of the secondary outcomes. Of the 14 adverse events in the tPA and DNase group, 6 (43%) were serious; of the 21 adverse events in the tPA and placebo group, 8 (38%) were serious. There were no deaths.

CONCLUSIONS AND RELEVANCE The addition of DNase to intrapleural tPA for children with pleural empyema had no effect on hospital length of stay or other outcomes compared with tPA with placebo. Clinical practice guidelines should continue to support the use of chest tube insertion and intrapleural fibrinolytics alone as first-line treatment for pediatric empyema.

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Up to 50% of children admitted to a hospital with community-acquired pneumonia develop an associated parapneumonic effusion. While the underlying infection often improves with antibiotics alone, some effusions become purulent and/or loculated, a condition known as pleural empyema. Recent estimates suggest a rate of 2.0 hospital discharges related to empyema per 100,000 children in the United States. Similar estimates have been reported in other countries.

Clinical practice guidelines recommend that children with empyema undergo pleural drainage if they have moderate to large pleural effusions or significant respiratory compromise. Pleural drainage options include decortication and drainage via video-assisted thoracoscopic surgery (VATS) or insertion of a chest tube with instillation of intrapleural fibrinolytics, such as tissue plasminogen activator (tPA). Systematic reviews of small randomized clinical trials of children with pleural empyema have reported similar outcomes with these 2 approaches but increased costs associated with upfront VATS.

Dornase alpha (DNase) has been shown in vitro to decrease viscosity by cleaving free DNA and liquefying pus in the pleural space. The nebulized formulation is approved for use in children with cystic fibrosis to facilitate airway clearance. A factorial randomized clinical trial of 210 adults with pleural empyema reported improved outcomes with the use of DNase and tPA compared with tPA alone, DNase alone, or normal saline flushes only. This included greater resolution of pleural opacity on chest radiography, decreased rate of referral for surgical debridement, and shorter length of stay in hospital. However, it remains unclear whether these findings can be extrapolated to children.

We designed the Intrapleural DNase and Tissue Plasminogen Activator in Pediatric Empyema (DTPA) trial to assess the efficacy and safety of tPA and DNase in children with pleural empyema compared with tPA alone. Since the combination of tPA and DNase has been shown to improve outcomes in adults, we hypothesized that this treatment strategy would result in shorter lengths of stay in hospital for children compared with tPA alone. We also compared a variety of secondary and exploratory outcomes between the 2 treatment groups related to efficacy, safety, and cost.

Methods

Study Design

The DTPA trial was a multicenter, parallel-group, placebo-controlled, superiority randomized clinical trial involving 6 Canadian children’s hospitals (Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Montreal, Quebec; Children’s Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario; The Hospital for Sick Children, University of Toronto, Toronto, Ontario; McMaster Children’s Hospital, McMaster University, Hamilton, Ontario; Alberta Children’s Hospital, University of Calgary, Calgary, Alberta; and British Columbia’s Children’s Hospital, University of British Columbia, Vancouver, British Columbia). The study protocol was registered at ClinicalTrials.gov (NCT01717742) and published in full previously and is available in Supplement 1.

Randomization and Masking

Randomization was stratified by study site. Participants were randomized into treatment groups using a random allocation sequence facilitated by an off-site data coordination center (Applied Health Research Centre, Toronto, Ontario, Canada). An allocation ratio of 1:1 with random permuted blocks of size 2 and 4 was used within each site to ensure that the treatment groups were approximately the same size within each site and throughout the trial overall. A computer-based pseudorandom number generator was used to create treatment allocation tables.

After participant eligibility was confirmed and consent was obtained, the site coordinator assigned a unique study identification number in sequential order. The study identification number corresponded with the randomization table held in each hospital.

In this multicenter randomized clinical trial of 97 children with pleural empyema, there were no significant differences between those treated with tPA and DNase and those treated with tPA and placebo.

Key Points

**Question** Is intrapleural tissue plasminogen activator (tPA) and dornase alfa (DNase) beneficial in pediatric empyema compared with tPA alone?

**Findings** In this multicenter randomized clinical trial of 97 children with pleural empyema, there were no significant differences between those treated with tPA and DNase and those treated with tPA and placebo.

**Meaning** Guidelines should continue to support the use of chest tube insertion and intrapleural fibrinolytics alone as first-line treatment for pediatric empyema.
hospital's research pharmacy for dispensing open-label tPA and either blinded DNase or placebo. The biostatistician at the data coordination center maintained a secure master list of randomization codes and assigned treatments.

Participants, families, clinicians, outcome assessors, research assistants, study investigators, and those who administered study medications were blinded to treatment assignment. Study medications were formulated by research pharmacists as clear liquids in identical polyethylene syringes (ie, with the same packaging, color, and volume) to maintain blinding.

Procedures
Participants were randomized to either (1) intrapleural tPA (Roche), 4 mg, followed by 5 mL of normal saline (ie, placebo; control group) or (2) intrapleural tPA, 4 mg, followed by DNase (Roche), 5 mg (intervention group). Study drugs were administered once daily for 3 days. The first dose was typically given within 1 hour of chest tube insertion.

Safety data on DNase in children is derived from its currently licensed indication (nebulization at a dose of 2.5 to 5 mg once or twice daily) for the reduction of sputum viscosity in patients with cystic fibrosis. Since the stability of tPA-DNase admixture is unknown, medications were administered sequentially with a 1-hour dwell time after each drug.

In the tPA and DNase group, participants received tPA, 4 mg (dissolved in 20 mL of normal saline if the participant weighed 10 kg or more or in 10 mL of normal saline if less than 10 kg), followed by a normal 5-mL saline flush. The chest tube was clamped for 1 hour and then allowed to drain for another hour while on −20 cm H2O suction with underwater seal. The child then received DNase, 5 mg (dissolved in 20 mL of normal saline if the participant weighed 10 kg or more or in 10 mL of normal saline if less than 10 kg), followed by a normal 5-mL saline flush. The chest tube was again clamped for 1 hour and finally left to drain on −20 cm H2O suction with underwater seal until the next dose the following day. Similarly, in the tPA and placebo group, participants received tPA, 4 mg, followed by 5 mL of placebo (ie, normal saline) instead of DNase. The same procedures were followed for treatment volume, saline flushes, and dwell time.

Outcomes
The primary outcome was length of stay in hospital (measured in days) from chest tube insertion to discharge. Secondary outcomes included time from chest tube insertion to meeting discharge criteria (defined after chest tube removal as having no fever [temperature less than 38°C], normal respiratory rate for age, no hypoxia, and drinking fluids well), time from chest tube insertion to removal, fever duration, additional pleural drainage procedures (eg, additional chest tube insertion or rescue VATS), ventilatory support (including both invasive and non-invasive positive-pressure ventilation), hospital readmissions up to 3 months postdischarge, and cost. Estimates of total health care costs were based on the perspective of the public health care payer and incorporated charges for all medications, hospital stay (general ward and/or intensive care unit), and readmissions within 3 months of discharge from baseline. Data are reported in 2018 US dollars. We also reported serious adverse events. Serious bleeding was defined a priori as intrapleural bleeding resulting in a hemoglobin drop of greater than 2 g/dL (to convert to grams per liter, multiply by 10) or requiring a transfusion of packed red blood cells.

Exploratory outcomes included degree of opacification of the affected hemithorax on chest radiography closest to time of chest tube removal. We also reported total pleural drainage volume from chest tube insertion to removal as well as cumulative drainage at 24 hours and 48 hours after chest tube insertion.

Sample Size Calculation
In previous trials of pediatric empyema, the mean time to discharge following pleural drainage ranged from 6 to 15 days. A randomized clinical trial using tPA dosing identical to the DTPA trial reported a mean (SD) length of stay after chest tube insertion of 6.8 (2.9) days.

Based on discussions with clinical experts, hospital administrators, and parents of children with pleural empyema, a 2-day difference in length of stay between treatment groups was selected as representing a minimal clinically important difference. This threshold has been used in a previous trial of pleural empyema in children comparing chest tube insertion and intrapleural fibrinolytics with primary VATS. Assuming a type I error rate of .05 (2-sided), power (1 − β) of 90%, and an SD of 2.9 days for each group, this trial required at least 46 participants in each group (92 individuals total) to detect a difference in length of stay of 2 days.

Statistical Analysis
We performed hypothesis testing on the basis of intention to treat for the primary, secondary, and exploratory outcomes. The primary outcome (length of stay in hospital after chest tube insertion) was reported as the mean difference (with 95% CIs), and the independent t test was used to compare the 2 treatment groups. For secondary outcomes, χ2 tests were used for dichotomous variables and independent t tests for continuous variables. Costing differences were assessed with the Mann-Whitney rank sum test.

A secondary analysis was conducted adjusting for potentially important baseline covariates of the primary outcome with multivariable regression, including admission to the intensive care unit, bacterial identification in blood, and study site. An interim analysis was performed after 25 and 50 participants were recruited for safety review by the study’s independent data monitoring committee.

All P values were 2-tailed, and significance was set at a P value less than .05. Analyses were conducted using SAS version 9.4 (SAS Institute) and R version 3.5.1 (The R Foundation).

Results
Recruitment
Between March 4, 2013, and December 13, 2017, 379 children with pleural empyema were screened across 6 study sites (Figure 1). A total of 281 children were excluded. The most common reasons for exclusion were not requiring chest tube in-
insertion (n = 128), having already undergone a pleural drainage procedure (n = 42), other chronic or neurologic disorders (n = 64), or the parent or guardian declining to participate (n = 34).

Of the 98 children randomized, 1 individual was included erroneously, as this participant never met study inclusion criteria (ie, chest tube was not required) and was excluded from further analysis. Of the remaining 97 participants, 49 were assigned to the tPA and DNase group and 48 to the tPA and placebo group. All were included in the analysis in accordance with the intention-to-treat approach. Seven participants (2 assigned to tPA and DNase and 5 assigned to tPA and placebo) did not complete all 3 study treatments. Reasons for stopping treatment early were based on the decision of the attending physician (1 in the tPA and DNase group and 2 in the tPA and placebo), family preference (1 in the tPA and DNase group), or adverse events (3 in the tPA and placebo group).

Baseline Characteristics
Baseline characteristics are summarized in Table 1. The participants were a median (interquartile range) age of 52 (36-66) months with similar proportions of male participants (54% [52 of 97]) and female participants (46% [45 of 97]). The groups were similar in terms of demographic characteristics (age, sex, and race/ethnicity), previous health (asthma, prematurity, and weight), clinical baseline features (days in hospital prior to chest tube insertion, fever days, exposure to antibiotics prior to chest tube insertion, admission to the intensive care unit, pleural effusion size, radiographic opacification, and bacterial identification in blood or pleural fluid), and chest tube characteristics (mode of insertion, type of chest tube, and size). Most participants in both groups had greater than 50% opacification of the affected hemithorax.

Primary Outcome
The mean (SD) length of stay in hospital following chest tube insertion was 9.0 (4.9) days among participants assigned to the tPA and DNase group compared with 9.1 (5.3) days in the tPA and placebo group (Table 2). This corresponded to a mean difference of −0.1 days (95% CI, −2.0 to 2.1; P = .96). The results did not change after adjusting for admission to the intensive care unit, positive blood culture, and study site (eTables 1 and 2 in Supplement 2).

Secondary Outcomes
Analysis of the secondary outcomes is presented in Table 2. There were no differences in time from chest tube insertion to meeting discharge criteria, time to chest tube removal, fever duration, frequency of needing invasive or noninvasive ventilatory support, need for additional pleural drainage procedures, or hospital readmission. Total costs were also comparable between the 2 groups (eTable 3 in Supplement 2).
Most participants in both groups (91 of 97 [94%]) were successfully managed with a single chest tube insertion followed by intrapleural tPA and either DNase or placebo. Only 6 participants required additional pleural drainage procedures. In the tPA and DNase group, 1 participant underwent rescue VATS, 2 participants underwent a second chest tube insertion alone, and 1 participant underwent insertion of a second and then a third chest tube. In the tPA and placebo group, 1 participant underwent rescue VATS alone and another underwent rescue VATS followed by chest tube insertion as a third procedure. Differences between treatment groups were not statistically significant.

Adverse events are summarized in Table 3. Similar numbers of participants experienced at least 1 adverse event in the 2 treatment groups (24% [12 of 49] vs 29% [14 of 48]; P = .64). The most common serious adverse event was serious bleeding. One participant assigned to the tPA and DNase group experienced a tension pyothorax, and another developed a bronchopleural fistula. One of the participants assigned to the tPA and placebo group experienced septic shock. There were no deaths in either group.

### Exploratory Outcomes

In both the tPA and DNase group and tPA and placebo group, most participants had opacification of the affected hemithorax less than or equal to 50% on chest radiography closest to time of chest tube removal (35 of 49 [71%] vs 43 of 48 [90%]; P = .42). The median (SD) overall volume of pleural drainage following chest tube insertion was also similar (1524 [909] mL vs 1733 [1029] mL; mean difference, −208.7 mL; 95% CI, −602.3 to 185.0; P = .30) and was also similar after 24 hours (741 [545] mL vs 809 [577] mL; mean difference, −67.6 mL; 95% CI, −300.0 to 164.9; P = .56) and 48 hours (957 [572] mL vs 1067 [674] mL; mean difference, −110.5 mL; 95% CI, −364.0 to 143.1; P = .39). These results are summarized in Table 2 and Figure 2.

### Discussion

To the best of our knowledge, this study is the first randomized clinical trial to explore the efficacy, safety, and cost of intrapleural DNase in children with pleural empyema. We found that treatment with tPA and DNase compared with tPA and placebo was not associated with an improvement in the primary outcome, length of stay in hospital. Furthermore, the confidence limits around the estimated difference between groups was within what we considered a clinically meaningful difference (ie, 2 days). We also found comparable results for all secondary and exploratory outcomes.

These findings contrast with the factorial randomized clinical trial of adults with pleural empyema, which reported improved outcomes with the use of tPA and DNase compared with tPA alone, DNase alone, or normal saline flushes only. These included greater resolution of pleural opacity on chest radiography, decreased rate of referral for surgical debridement, and shorter length of stay in hospital.

There are several possible explanations for the different findings in the adult trial and the current study. First, empy-
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Original Investigation Research

simultaneously with no apparent effect on outcomes.28-30 There have been some recent reports of administering both medications, but there is no clinical trial evidence for the use of tPA in children.4 There have been some recent reports of administering both medications simultaneously with no apparent effect on outcomes.28-30

Limitations

This study has some important limitations. First, our standard deviation for length of stay in hospital was larger in the study than what was predicted based on the results of previous studies. In the study protocol, we estimated an SD of 2.9 days, whereas in the actual trial, the value was 5.1 days. This finding may have decreased our ability to detect a difference (if one actually existed). Nevertheless, given the nearly identical lengths of stay between the 2 treatment groups, our limit of confidence was within the predefined threshold for a minimally clinically important difference of 2 days. Second, we designed this trial using a pragmatic approach.31 While this design has a number of benefits by simulating real-world applicability, it weakens our ability to attribute the lack of difference between the groups as being due to DNase as opposed to systematic differences in the use of cointerventions across the 2 groups.32 Although participating hospitals received suggestions for standard care, we made no attempt to ensure that suggestions for chest tubes size, length or type of antibiotic treatment, or other aspects of routine care were implemented.23 This explanation for our null observation, while possible, is unlikely given the similarities in the 2 groups at baseline, rigorous blinding and randomization procedures, and the lack of effect on the primary outcome when adjusted for study site and other confounders. Third, some participants withdrew from the study before completing all 3 study treatments.

Fourth, while we collected a wide variety of measures, we did not assess some potentially important outcomes, such as pain, patient satisfaction, and degree of resolution on chest radiography for each participant. Radiographic resolution was

### Table 2. Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%)</th>
<th>tPA and DNase (Intervention Group) (n = 49)</th>
<th>tPA and Placebo (Control Group) (n = 48)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay from chest tube insertion to discharge, mean (SD), d</td>
<td>9.0 (4.9)</td>
<td>9.1 (5.3)</td>
<td>−0.1 d (−2.0 to 2.1)</td>
<td>.96</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from chest tube insertion to meeting discharge criteria, mean (SD), d</td>
<td>8.2 (4.5)</td>
<td>8.5 (5.4)</td>
<td>−0.3 d (−1.7 to 2.3)</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>Time from chest tube insertion to removal, mean (SD), d</td>
<td>6.9 (4.3)</td>
<td>6.9 (5.3)</td>
<td>0 d (−2.0 to 2.0)</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>Fever duration after chest tube insertion, mean (SD), d</td>
<td>2.8 (3.4)</td>
<td>3.3 (3.4)</td>
<td>−0.5 d (−0.9 to 1.9)</td>
<td>.46</td>
<td></td>
</tr>
<tr>
<td>Ventilatory support after chest tube insertion</td>
<td>9 (18)</td>
<td>8 (17)</td>
<td>1.7% (−13.4 to 16.8)</td>
<td>.83</td>
<td></td>
</tr>
<tr>
<td>Additional pleural drainage procedures</td>
<td>4 (8b)</td>
<td>2 (4)c</td>
<td>4.0% (−5.5 to 13.5)</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td>Additional chest tube(s) only</td>
<td>3 (6)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Rescue VATSd</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Hospital readmissions</td>
<td>2 (8)</td>
<td>0</td>
<td>8.3% (−2.7 to 19.4)</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>Total cost, mean (SD), 2018 US $e,f</td>
<td>11 329 (7139)</td>
<td>10 760 (5071)</td>
<td>$1456 (−1910 to 4822)</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td><strong>Exploratory outcome</strong></td>
<td></td>
<td></td>
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<tr>
<td>Degree of opacification on chest radiography prior to chest tube removal, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>24 (49)</td>
<td>33 (69)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-50</td>
<td>11 (22)</td>
<td>10 (21)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-75</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>NA</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>7 (14)</td>
<td>3 (6)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DNase, dornase alfa; NA, not applicable; tPA, tissue plasminogen activator; VATS, video-assisted thoracoscopic surgery.

a Positive-pressure ventilation includes endotracheal intubation and mechanical ventilation as well as noninvasive ventilatory support.
b One participant underwent rescue VATS, 2 participants underwent a second chest tube insertion alone, and 1 participant underwent a second and then a third chest tube insertion.
c One participant underwent rescue VATS alone and another underwent rescue VATS followed by chest tube insertion as a third procedure.
d Decortication via VATS.
e Total cost includes medications (CaD $396 [US $297] for tPA and CaD $240 [US $180] for DNase), hospital admission, and readmissions within 3 months.
f Costs were converted from 2018 Canadian dollars to 2018 US dollars using the approximate exchange rate in July 2018 (0.75 CaD to 1 USD).

Inventra is a different disease in children compared with adults. Children with empyema are often previously healthy with few or no preexisting comorbidities. They have lower rates of needing rescue surgical therapy, and their long-term outcomes are almost always complete recovery with a near-zero rate of mortality.25-27 In the current study, this difference was further amplified by the fact that we specifically excluded children with serious long-term comorbidities. Participants in the adult trial had a variety of comorbidities, and the mortality rate was 11% after 12 months of follow-up.22 Another difference between these studies was the dosing regimen. While both studies administered tPA and DNase separately and sequentially with identical dwell times, medications in the adult study were administered twice per day for 3 days (ie, a total of 6 doses each), and the dosing of tPA differed (4 mg in the current trial vs 10 mg in the adult trial), although the dosing of DNase was identical. We elected to administer drugs once daily for 3 days at the prespecified dose to conform with standard practice and clinical trial evidence for the use of tPA in children.4

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Conclusions

Taken together, the results of this multicenter randomized clinical trial provide no evidence of a difference in outcomes between children treated with 3 doses of sequentially administered tPA and DNase compared with tPA and placebo. Guidelines should continue to support the use of chest tube insertion and intrapleural fibrinolytics alone as first-line therapy for a primary outcome in the adult trial of tPA and DNase vs tPA and placebo, defined by changes in radiography from baseline to day 7 and validated using a computed tomography digital measurement model. Our study team felt it would be ethically inappropriate to expose children to additional ionizing radiation beyond their routine clinical care and so did not include standardized radiography in the protocol. Nevertheless, the degree of opacification for all available chest radiography at baseline and again prior to chest tube removal was similar in both groups.
children with empyema and should not recommend the routine use of DNase. This study also serves as a cautionary reminder that children are not just little adults and that extrapolating evidence from adult trials to children may be problematic, particularly when the same disease may have different epidemiology, risk factors, and outcomes.

**REFERENCES**


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**Author Contributions:** Mr Thorpe and Dr Cohen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Intrapleural Tissue Plasminogen Activator and Domase Alfa in Pediatric Empyema


