Efficacy of standardizing fibrinolytic therapy for parapneumonic effusion

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Abstract

Background While chest tube placement with pleural fibrinolytic medication is the established treatment of pediatric empyema, treatment failure is reported in up to 20% of these children.

Objective Standardizing fibrinolytic administration among interventional radiology (IR) physicians to improve patient outcomes in pediatric parapneumonic effusion.

Materials and methods We introduced a hospital-wide clinical pathway for parapneumonic effusion (1–2 mg tissue plasminogen activator [tPA] twice daily based on pleural US grade); we then collected prospective data for IR treatment May 2017 through February 2020. These data included demographics, co-morbidities, pediatric intensive care unit (PICU) admission, pleural US grade, culture results, daily tPA dose average, twice-daily dose days, skipped dose days, pleural therapy days, need for chest CT/a second IR procedure/surgical drainage, and length of stay. We compared the prospective data to historical controls with IR treatment from January 2013 to April 2017.

Results Sixty-three children and young adults were treated after clinical pathway implementation. IR referrals increased ($P = 0.02$) and included higher co-morbidities ($P = 0.005$) and more PICU patients ($P = 0.05$). Mean doses per day increased from 1.5 to 1.9 ($P < 0.001$), twice-daily dose days increased from 38% to 79% ($P < 0.001$) and median pleural therapy days decreased from 3.5 days to 2.5 days ($P = 0.001$). No IR patients needed surgical intervention. No statistical differences were observed for gender/age/weight, US grade, need for a second IR procedure or length of stay. US grade correlated with greater positive cultures, need for chest CT/second IR procedure, and pleural therapy days.

Conclusion Interventional radiology physician standardization improved on a clinical pathway for fibrinolysis of parapneumonic effusion. Despite higher patient complexity, pleural therapy duration decreased. There were no chest tube failures needing surgical drainage.

Keywords Chest tube · Children · Clinical pathway · Empyema · Fibrinolytic · Interventional radiology · Parapneumonic effusion · Tissue plasminogen activator

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Introduction

Chest tube placement with pleural fibrinolytic medication administration has been established as an effective first-line treatment option in pediatric pneumonia with complicated pleural effusion [1–5]. Pleural infection includes parapneumonic effusion and empyema occurring along a continuum that is often divided into three stages: exudative/simple, fibrinopurulent and organizational [6–8]. Indications for chest tube placement include both complicated parapneumonic effusions and empyema; these indications overlap and their outcomes are typically reported as a group [9]. Reported fibrinolytic dosing has been empirical, weight-based or stratified based on pleural US complexity [3, 4, 10, 11]. While planned frequency of reported dosing has been once, twice or three times daily, data on actual pleural doses administered per day during fibrinolytic therapy are lacking in the published literature. Because pleural instillation of the medication into the chest tube is dependent on bedside presence of the interventional radiology physician or physician extender in most hospitals, actual pleural doses delivered per day can be markedly fewer than the planned dose frequency following chest tube insertion.

Society of Interventional Radiology (SIR) guidelines on parapneumonic effusion/pediatric empyema reported a chest tube failure rate of 7–20% where additional surgical pleural drainage (video-assisted thoracoscopic surgery, or VATS) was required [9]. Clinical pathways are tools to translate evidence into local care of a specific clinical condition; treatment steps are delineated to safely standardize care among various clinical providers [12, 13]. Following a multidisciplinary plan has been found to reduce treatment variation, increase clinical efficiency and in some instances reduce hospital stay and hospital costs [12–14]. Previously at our institution the frequency of interventional radiology (IR) rounding and daily dosing decisions in IR patients with chest tube for parapneumonic effusion were variable and left to individual IR physician judgment and preference. The goal of this study was to prospectively follow IR physician fidelity to a newly instituted hospital-wide clinical pathway for pediatric parapneumonic effusion and evaluate patient outcomes.

Materials and methods

Following a root-cause analysis of a patient safety event pertaining to treatment variation in pediatric parapneumonic effusion, our hospital administrators sought multidisciplinary input from all services treating children with complicated pneumonia at our single tertiary referral children’s hospital. These services included the Emergency Department, Infectious Disease, IR, Nursing, Pediatric Hospitalists, Pediatric Intensive Care Unit (PICU) and Surgery. Following monthly meetings for 8 months facilitated by the clinical project manager in the Quality, Risk and Safety Department, a hospital-wide clinical pathway for treatment of parapneumonic effusion was instituted in May 2017. In this pathway, a majority of chest tube insertion requests for parapneumonic effusion are steered to the IR team (Fig. 1); PICU physicians can either place the chest tube or consult the IR team for chest tube placement in parapneumonic effusion.

Institutional review board (IRB) approval allowed for prospective data collection and entry into an existing IR database (Excel; Microsoft, Redmond, WA) of consecutive children and adolescents with IR chest tube placement for parapneumonic effusion. This prospective study was preceded by a 4-year IRB-approved retrospective quality-improvement project of IR service performance. IRB approval was obtained to collect data on pediatric patients treated by the IR service (inclusion criteria); data were not collected on patients with chest tubes placed by PICU physicians (exclusion criteria). Patient demographic data included gender, age, weight, co-morbidities (additional services consulted other than IR and Infectious Disease), and need for PICU admission. Prospective data collection included pleural fluid culture results, daily pleural dose average, twice-daily dose days, skipped dose days, pleural therapy days, need for chest CT while on the pathway, need for a second IR pleural procedure, need for surgical drainage and length of hospital stay.

Complexity of the pleural effusion was determined before the IR procedure and based on a pleural US grade (grade 1, less than 50% pleural echogenicity; grade 2, greater than 50% pleural echogenicity; graded at the most complex interspace level) previously developed by our IR team and reported in 2016 [10]. The prospective study period was from May 2017 to February 2020 (concluding a month before any documented cases of coronavirus disease 2019 [COVID-19] in our state). We compared these prospective data to historical controls — patients with parapneumonic effusion treated, and in part reported, by the same IR team at this institution from January 2013 to April 2017 [10].

Standard IR procedure was chest tube placement under US and fluoroscopic guidance in the IR lab. Most tubes were placed via a lateral chest wall entry site, the “safe triangle” [6, 9], and a few tubes were placed into subpulmonic, apical or posterior locations as guided by pre-procedure imaging. The tube of choice for primary chest tube placement in the prospective study was a 10.2-French (Fr) Dawson-Mueller drainage catheter (Cook Medical, Bloomington, IN) as in the historical control group; a smaller tube (8.5-Fr Dawson-Mueller drainage catheter;
Cook Medical) was allowed in children under 10 kg, and larger 12-Fr tubes (Multipurpose Drainage Catheter, Cook Medical) were allowed in obese children and those with thick pleural drainage. Pleural fluid aspirate sample was sent for gram stain/culture in all patients; this included polymerase chain reaction (PCR) testing. Pleural glucose, lactase dehydrogenase and cell count were infrequently ordered in these prospective patients and were not evaluated in this study; point-of-care pleural pH testing is not established in our IR lab. Pleural tPA alteplase (Activase; Genentech, South San Francisco, CA) dosing was initiated in the IR Lab, with the first dose given following chest tube insertion and withdrawal of as much pleural fluid that could be easily aspirated via syringe. We had no milliliter per kilogram limit of pleural fluid to withdraw in this initial tube placement procedure. Pleural tPA dosing was 1 mg or 2 mg twice daily based on pre-procedure diagnostic US grade (grade 1, 1 mg; grade 2, 2 mg) and was followed with a normal saline tube flush based on patient size (10 mL in those >10 kg; 5 mL in those <10 kg). Following pleural medication administration, the chest tube stopcock was closed to external drainage for 1 h before initiating wall suction via water seal (Ocean Water Seal Chest Drain, Atrium Medical Corp., Merrimack, NH) per hospital protocol (20-cm water in patients older than 5 years, 15-cm water in children 1–5 years, 10-cm water in children younger than 1 year).

If the IR chest tube placement was in the afternoon or evening, the next pleural tPA dose was planned for the following morning. Bedside chest tube fibrinolytic medication was instilled by an IR physician, an IR physician extender/registered radiology assistant, or a radiology trainee on the IR elective (radiology resident, pediatric radiology fellow or IR fellow) under the supervision of the IR staff. In addition to charting in the electronic medical record (Epic, Verona, WI), a daily tPA dosing calendar...
was displayed in the IR suite to document compliance with the twice-daily dose expectation.

With IR physician staff turnover (one staff relocation, one staff retirement, three new staff recruitments), three IR physicians established in the pathway and three IR physicians new to the pathway participated over the 2.8-year prospective study period. New IR physicians starting on staff during the study period were educated on this team’s experience treating parapneumonic effusion and instructed to follow the new hospital-wide clinical pathway, regardless of their years of IR staff experience [10].

The endpoint of IR pleural therapy included improved respiratory status, pleural displacement <5 mm on chest radiograph and declined chest tube output (<0.5 mL/kg over a 12-h period). Fever and oxygen requirement were expected to resolve unless associated necrotizing pneumonia was detected on chest CT performed on the pathway. All patients were followed from the time of initial IR referral to hospital discharge to evaluate for procedure complications, complications of fibrinolytic therapy, and any pleural abnormalities requiring an additional drainage procedure, and to document length of hospital stay.

Statistical analyses included Mann–Whitney tests to compare median values and two-sample t-tests to compare mean values. Percentages were compared with a Fisher exact test. We compared the average rate of referrals for IR chest tube insertion for parapneumonic effusion in the pre- and post-pathway periods using a test for homogeneity of Poisson rates. We analyzed the data using the software package StatXact-12 (version 12.0; Cytel Studio, Cytel Inc., 2019). P ≤ 0.05 was considered statistically significant.

**Results**

We included 63 consecutive children and adolescents with IR chest tube for parapneumonic effusion in this prospective study period following initiation of the clinical pathway. We compared the data to that of 63 patients with IR chest tube for parapneumonic effusion placed by the same IR team and whose retrospective data were collected prior to the initiation of the clinical pathway. No patients had missing data values of the variables studied.

The prospective study range was 33 months, compared to 51 months for the retrospective study. Patient characteristics (gender, age, weight) in the prospective study group did not differ from those in the control group (Table 1). In this pediatric study at a children’s hospital, the median patient age was 5.8 years post-pathway and 5.4 years pre-pathway. Only one patient (1/63, 1.6%) was older than 18 years in the prospective post-pathway group, while seven patients (7/63, 11.1%) were older than 18 years in the pre-pathway group. While 59/63 (93.7%) patients received the standard 10.2-Fr Dawson-Mueller drainage catheter, 1 child under 10 kg received an 8.5-Fr Dawson-Mueller drainage catheter and 3 received a 12-Fr Multipurpose Drainage Catheter based on large patient size (130 kg) or thick pleural pus. No patients in this study developed re-expansion pulmonary edema relating to chest tube placement and withdrawal of pleural fluid.

Interventional radiology referrals for chest tube insertion for parapneumonic effusion increased from 1.2/month to 1.9/month on the clinical pathway (P = 0.02). Although US grade complexity did not differ between the groups (P = 0.36), patients in the prospective group had higher co-morbidities (P = 0.005) and more often required PICU

| Table 1 Patient characteristics |
|----------------------------------|
| Variable                        | Before clinical pathway (n = 63) | On clinical pathway (n = 63) | P-value* |
| Gender, male, n (%)            | 38 (60.3%)                     | 32 (50.8%)                   | 0.37     |
| Age (mos.)                     | Mean (SD) 65 (1.5, 403)        | Median (min, max) 70 (4, 237) | 0.93     |
| Weight (kg)                    | Mean (SD) 34.2 (29.6)          | Median (min, max) 21.0 (4, 119) | 0.52     |
| Children with ≥ 1 comorbidity, n (%) | 42 (66.7%) | Median (min, max) 20.9 (6.5, 126) | 0.62     |
| Children in PICU, n (%)        | 22 (34.9%)                     | 34 (54.0%)                   | 0.05     |
| Ultrasound grade               | Grade 1, n (%)                 | 28 (44.4%)                   | 0.36     |
|                                | Grade 2, n (%)                 | 35 (55.6%)                   |          |

kg kilogram, max maximum, min minimum, mos. months, n number, PICU pediatric intensive care unit, SD standard deviation
* P-value ≤ 0.05 is significant (bold)
admission ($P = 0.05$). Note that IR patients treated in this prospective study included all three stages of parapneumonic effusion and empyema: exudative/simple, fibrinopurulent and organizational. Pleural culture results including PCR testing were available in all patients. A pleural organism was identified in 32 of 63 (50.8%) subjects, and this did not differ from the control group ($P = 0.72$). The most frequent organisms identified were *Streptococcus pneumoniae* ($n = 12$), *Staphylococcus aureus* ($n = 6$) and other Streptococcus series ($n = 5$), which was similar compared to historical control group ($P = 0.72$). These IR procedures consisted of drain exchange (tube upsize to 12 Fr or 14 Fr) for declining drainage and respiratory status with opacified hemithorax on follow-up chest radiograph (4/12 patients) or new chest tube placement for undrained pleural collection detected on follow-up intravenous (IV)-contrast-enhanced chest CT (8/12 patients).

Median length of hospital stay was 11 days and did not differ from the control group ($P = 0.56$). Patients with grade 2 US in this prospective study were more likely to have a positive culture, require a chest CT, need a second IR drainage procedure and have longer pleural air collection several days after IR chest tube placement; this hydropneumothorax was a known sequela of necrotizing pneumonia (bronchopleural air leakage) and was not a chest tube complication in this patient. No additional symptomatic bronchopleural fistulas were detected in the study period. No IR procedure complications or complications of pleural fibrinolytic therapy occurred. When IR management was completed, no recurrence of pleural abnormality requiring treatment occurred during the hospital stay in the prospective study group (hospital stay range 3–90 days, total group hospital stay: 896 days). No IR patients needed surgical intervention after implementation of the clinical pathway, Hospital stay for these patients was 896 days. No IR patients needed surgical intervention after implementation of the clinical pathway, or new chest tube placement for undrained pleural collection detected on follow-up intravenous (IV)-contrast-enhanced chest CT (8/12 patients).

| Variable                      | Before clinical pathway ($n = 63$) | On clinical pathway ($n = 63$) | $P$-value$^a$ |
|-------------------------------|-----------------------------------|-------------------------------|--------------|
| IR referrals/month            | 1.2                               | 1.9                           | 0.02         |
| tPA doses/day                 | 1.5 (0.5)                         | 1.9 (0.2)                     | <0.001       |
| Mean (SD)                     | 1.5 (0.5)                         | 1.9 (0.2)                     | <0.001       |
| Median (min, max)             | 1.4 (0.3, 2.0)                    | 2 (1.3, 2.3)                  | <0.001       |
| BID dose days, n (%)          | 24 (38.1%)                        | 50 (79.4%)                    | <0.001       |
| Days of tPA therapy           | 4.1 (2.5)                         | 2.8 (1.4)                     | <0.001       |
| Mean (SD)                     | 4.1 (2.5)                         | 2.8 (1.4)                     | <0.001       |
| Median (min, max)             | 3.5 (1, 12)                       | 2.5 (0.5, 7)                  | 0.001        |
| Patients with skipped dose    | 16 (25.4%)                        | 7 (11.1%)                     | 0.06         |
| days, n (%)                   | 16 (25.4%)                        | 7 (11.1%)                     | 0.06         |
| Culture or PCR positive, n (%)| 35 (55.6%)                        | 32 (50.8%)                    | 0.72         |
| Patients needing 2nd IR       | 11 (17.5%)                        | 12 (19.0%)                    | 1.0          |
| procedure, n (%)              | 11 (17.5%)                        | 12 (19.0%)                    | 1.0          |
| Length of stay (days)         | 19.3 (30.0)                       | 14.4 (13.7)                   | 0.24         |
| Mean (SD)                     | 19.3 (30.0)                       | 14.4 (13.7)                   | 0.24         |
| Median (min, max)             | 11 (4, 222)                       | 11 (3, 90)                    | 0.56         |

*BID twice a day, IR interventional radiology, max maximum, min minimum, PCR polymerase chain reaction, SD standard deviation, tPA tissue plasminogen activator

$^a P$-value $\leq 0.05$ is significant (bold)
compared to 1.6% (1/63) needing surgical VATS drainage before the clinical pathway.

**Discussion**

Our study shows that IR physicians managed parapneumonic effusions in a more standardized fashion following implementation of a hospital-wide clinical pathway. Despite higher complexity of increased IR referrals, pleural therapy duration decreased and need for surgical intervention was eliminated.

Image-guided chest tube placement with pleural instillation of fibrinolytic medication is an established treatment of pediatric pneumonia with complicated pleural effusion or empyema [1–5]. While small-caliber drains are effective and well tolerated, the chest tube failure rate with pleural fibrinolysis is reported in up to 20% of cases in a
quality improvement standards publication of the Society of Interventional Radiology, leaving ample room for practice improvement [9, 16–19]. Empirical, weight-based or US-stratified pleural fibrinolytic dosing regimens have been reported (once daily, twice daily, thrice daily) [3, 4, 10, 11].

Variation in chest tube management is common; dosing preferences and rounding expectations might differ when introducing new physicians trained at other institutions. In addition, actual adherence of bedside pleural dose administration to a chosen dosing frequency plan might be incomplete for many reasons, including an impression by a given physician that pleural therapy has been completed (resolving patient symptoms/declining drain output/reduced radiographic pleural displacement). Inconsistent IR clinical rounding with skipped doses of pleural fibrinolytic medication can prolong the chest tube duration and lead to the need for additional resources including surgical team consultation and potential VATS drainage [1, 5, 10, 20].

Clinical pathways are tools formed with multidisciplinary input to provide a structured plan for managing a specific clinical condition [12, 13]. Pathway development includes identifying a practice area needing improvement, building a multidisciplinary work team, defining a specific diagnosis, reviewing pertinent literature, and developing a clinical pathway; this is followed by implementation of the clinical pathway and ongoing evaluation of the pathway’s impact [12]. By standardizing sequential treatment steps among providers and recommending timing of potential interventions, clinical efficiency should increase, treatment delays should decrease and hospital stay/hospital cost might be reduced [12–14]. Follow-up review of the clinical pathway is important to assess performance and need for potential adjustments [9]. Based on clinical experience and additional published evidence, the timing of contrast-enhanced chest CT on our clinical pathway — to evaluate for undrained pleural components (which might need IR drain repositioning or surgical VATS) and detect lung parenchymal changes of necrotizing pneumonia — was shortened to occur after 3 days of pleural fibrinolytic therapy (initial pathway timing of chest CT was after 4 days of pleural fibrinolytic therapy, Fig. 1) [5, 14–17]. Further, the goal of pleural fibrinolysis duration on the clinical pathway was revised in 2021 because 12/21 (57.1%) grade 1 US patients required fewer than the protocol goal of 2–3 pleural treatment days and 17/42 (40.5%) grade 2 US patients required fewer than 3 days of pleural alteplase therapy. Past reports of clinical pathways for pediatric empyema at children’s hospitals and across hospital networks have been shown to improve patient care and guide eventual need for surgical drainage and potentially decrease length of stay [6, 16, 21]. It was our goal to standardize care of pediatric parapneumonic effusion throughout our children’s hospital with a new clinical pathway involving image-guided small-bore pigtail chest tube placement with twice-daily pleural fibrinolytic dosing based on pre-procedure US grade complexity [5, 22]. This pathway ensures the primary care service at our institution that the IR team will make two consistent bedside visits each day following the chest tube procedure. These two visits allow the IR physician or supervised designee to administer the fibrinolytic medication and verify adequate function of the chest tube: confirming adequate wall suction, detecting inadvertent tube stopcock closure and confirming that the tube is not kinked or clogged [10, 18, 19, 23, 24]. On the contrary, if once-daily IR rounding is the expectation, a child with a skipped bedside visit might not be re-evaluated for 40 h or more. These twice-daily rounding duties can be shared with a physician extender working within a scope of practice under a supervising IR physician [25]. The rounding IR physician also guides the primary care team on appropriate utilization of follow-up imaging (non-daily chest radiographs tailored to clinical status and chest CT with IV contrast agent when indicated per the clinical pathway) [5, 15, 24]. IR physician knowledge of imaging findings of necrotizing pneumonia is important because this condition can cause prolonged respiratory compromise and fever after a majority of pleural fluid has been effectively drained [15].

After implementing this pathway, the number of IR referrals for chest tube insertion increased significantly and included children with higher co-morbidities and more frequent PICU admissions. During the 2.8-year prospective study duration, staffing turnover occurred, with three new pediatric IR staff physicians seamlessly incorporated into pathway utilization; with basic education provided to these new physicians, the care remained consistent and improved compared to our IR service performance before the clinical pathway was implemented. The mean 1.9-dose daily average nearly reached the twice-daily pathway goal (Fig. 2) and duration of chest tube therapy was reduced. Despite treating more complex patients with a higher percentage needing PICU care, the length of hospital stay did not increase compared to that for less complex patients treated before the clinical pathway was instated. No surgical intervention was required in our prospective IR cohort, a performance not reported at other centers [6, 9, 17, 24].

There were some limitations to this study. One limitation is that the end point of pleural fibrinolytic therapy involves individual physician judgment. A rounding IR physician might see patient improvement on this clinical pathway and hold additional pleural fibrinolytic doses before pleural therapy is completed; patient assessment on subsequent days might reveal the need for additional pleural medication and result in a day of skipped pleural tPA dosing. The addition of three new IR physicians over the course of the prospective study certainly added variability into our technique of chest tube insertion and subsequent post-procedure management; however, such variability should further emphasize the
need for a standardized clinical pathway. Despite the positive impact on many outcome measures, we did not address the impact of this clinical pathway on hospital charges/hospital costs [11, 26]. Last, outcome results included only the group of parapneumonic effusions treated by the IR physicians (per approved IRB protocol); corresponding data in children receiving PICU team chest tube placement with subsequent PICU physician pleural tPA administration were not collected.

Conclusion

Interventional radiology physician standardization improved on a clinical pathway for fibrinolysis of parapneumonic effusion. Despite higher patient complexity, pleural therapy duration decreased.

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Declarations

Conflicts of interest  None

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