

Streptokinase Fibrinolysis Protocol: The Advantages of a Non-Operative Treatment for Stage II Pediatric Empyema Patients

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ABSTRACT: **Background:** Pediatric empyema necessitates prompt resolution and early hospital discharge with minimal morbidity. However, the most effective treatment approach is not yet established.

Objectives: To assess the efficacy of an intrapleural streptokinase washing protocol as a non-operative treatment for stage II pediatric empyema as compared to operative decortications, by the number of pediatric intensive care unit (PICU) admissions, length of PICU stay, and hospitalization duration.

Methods: We retrospectively evaluated 75 consecutive pediatric empyema cases for the period January 2006 to December 2009. Since July 2007 we have used repeated streptokinase-based pleural washing for stage II patients whose condition did not improve with chest drainage.

Results: Before July 2007, 17 of 23 stage II empyema patients underwent decortication, compared to only 1 of 21 after July 2007. Non-operated children were admitted to the PICU less frequently than those who were operated (83% vs. 31%, $P = 0.0006$) and spent less time in the PICU (2.56 ± 1.92 vs. 1.04 ± 1.9 days, $P = 0.0148$); there was no significant statistical difference in overall hospitalization (13.33 ± 3.69 vs. 11.70 ± 5.74 days, $P = 0.301$).

Conclusions: Using intrapleural streptokinase washing as a non-operative treatment for stage II pediatric empyema yielded comparable success rates to the operative approach, with less morbidity.

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KEY WORDS: pediatric empyema, stage II empyema, fibrinolysis, streptokinase, pediatric intensive care unit (PICU)

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Pediatric empyema is increasing [1]. Analogous to the treatment in adults, pediatric empyema management includes the use of antibiotics, chest drainage and a variety of surgical techniques for empyema resolution and lung decortication. Still, there is ongoing controversy regarding the most suitable treatment approach for the pediatric population, namely operative vs. non-operative [1-4].

Thrombolytic agents for intrapleural washing were first administered some 60 years ago [5-7]. Fibrinolytic agents work by decreasing fibrinous strands and reopening pleural pores blocked by fibrinous material, thereby permitting pleural resorption. Intrapleural fibrinolytic therapy may be an efficient substitute for surgery and has been reported to be a useful adjunct to accelerate drainage of loculated effusions in complicated empyema [8,9]. The most commonly used fibrinolytic agents in the clinic are streptokinase, urokinase and tissue plasminogen activator. Although fluctuating success rates have been attributed to all these fibrinolytic agents [10-13], in the current study we used streptokinase based on reports of fewer adverse effects and higher success rates [4-16]. To date, the optimal dosage and required number of daily washings of streptokinase are still under debate and require further investigation [14].

Accordingly, the aim of the present study was to evaluate the clinical success of a strict and uniform protocol of intrapleural streptokinase washing among stage II pediatric empyema patients as compared to the surgical approach practiced in our hospital. This assessment was based on admission frequency to the pediatric intensive care unit, duration of stay, and overall hospitalization time. Additional aspects and benefits of the non-surgical approach in the pediatric empyema population were also addressed.

The surgical approach in our hospital at the time of the study was solely open decortication. Although video-assisted thoracic surgery is considered to have certain advantages over open surgery for treating pediatric empyema [17], the latter is more commonly used [1,17]. Therefore, comparing the efficacy of streptokinase treatment to that of surgery is a necessary step in the attempt to obviate operative procedures among pediatric empyema patients for whom open decortication is still the common practice.

PATIENTS AND METHODS

We retrospectively evaluated all cases of pediatric empyema admitted to our hospital from January 2006 to December 2009. The computerized medical records of these 75 consecutive cases were reviewed by a single investigator (D.L.F.).

Patients were divided into groups according to their empyema stage based on the 1962 classification of the American Thoracic Society [1]. Forty-four patients had stage II empyema, fibrinopurulent phase, and 31 patients had stage I empyema, parapneumonic effusion phase. All patients underwent an ultrasound, and patients with pleural drainage were diagnosed as empyema according to pleural fluids (pleural markers, such as pH, lactate dehydrogenase or culture/polymerase chain reaction). Exclusion criteria were age above 18 years, empyema due to causes other than pneumonia, and extreme cases of chronic illness that led to complex morbidity.

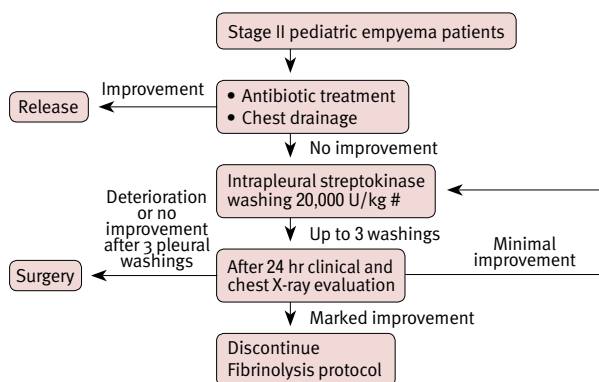
TREATMENT APPROACH

The goals of effective empyema treatment include infection and sepsis control, resolution of the empyema cavity, re-expansion of the underlying lung to restore function, and reduction in hospital stay [20]. Accordingly, the treatment approach for empyema usually involves antibiotic therapy, chest drainage with or without fibrinolytic agents, and early decortication surgery in phase II disease [20]. In July 2007 we adopted a more conservative approach for the treatment of pediatric empyema. Namely, we use repeated streptokinase fibrinolytic pleural washing for phase II patients whose condition did not improve with chest drainage alone. Surgery was reserved only for cases where fibrinolytic agents did not resolve the disease. The current study is based on the routine clinical practice initiated for reducing surgery in pediatric empyema patients. Therefore, no institutional approval was required for this study.

INTRAPLEURAL STREPTOKINASE WASHING PROTOCOL

Prior to July 2007 we used either streptokinase or urokinase as fibrinolytic agents according to different protocols. Since the success rates of these protocols fluctuated, we decided on a uniform practice. The chosen fibrinolytic pleural washing protocol [Figure 1] was initiated in July 2007 and comprised solely

Figure 1. The intrapleural streptokinase washing protocol for treatment of pediatric empyema patients



Under one year of age dose reduced to 10,000 U/kg

streptokinase (Streptase[®], 1,500,000 U, CSL Behring GmbH, Germany). The protocol involved the intrapleural administration of 20,000 U/kg streptokinase in patients aged 12 months or older and 10,000 U/kg in patients younger than 12 months. Pleural washings were performed by thoracic surgeons. Both doses were dissolved in 50 ml normal saline to allow a sufficient distribution of fibrinolytic substance in the pleural cavity. After each washing the chest drain was clamped for 4 hours and then reopened. No underwater seal suction was used. The washing was done once every 24 hours, usually on 3 consecutive days. The pleural space was evaluated each day using plain chest X-ray. The streptokinase protocol was terminated after the first or second washing if a dramatic clinical improvement was observed, namely resolution of fever and respiratory symptoms as well as a substantial decrease in drainage fluid volume, or if radiographic improvement was evident, i.e., a full lung re-expansion. If no improvement was observed after three washings, or if there was an obvious clinical deterioration, the surgical approach was applied. This involved the insertion by thoracic surgeons of large-bore silicone chest tubes, with the patient under conscious sedation. After the empyema treatment and recovery from pneumonia the patients were discharged. Full lung re-expansion was observed during an ambulatory follow-up at least one month after discharge.

DATA ANALYSIS

All analyses were conducted using JMP Version 8 (SAS Institute, Cary, NC, USA). To evaluate the clinical efficiency of the streptokinase washing protocol, three objective outcome measures were defined and compared in the two groups: pediatric empyema patients who were operated vs. those who were not. The outcome measures were the number of PICU admissions, length of PICU stay, and total hospitalization period. Group differences in these parameters as well as age, gender and operated site were evaluated using two-sided unpaired *t*-tests for independent samples and comparison of two independent proportions. Means and standard deviations were computed for the various parameters of the study data. Statistical significance was set at $P < 0.05$.

RESULTS

The clinical characteristics of the stage I and stage II empyema patients are summarized in Table 1. Thirty-one patients were diagnosed with stage I empyema, parapneumonic effusion phase, only one of whom was treated with pleural drainage; all patients fully recovered with empiric antibiotic treatment. Forty-four patients were diagnosed with stage II empyema. No significant differences were found between the operated and the non-operated group in age ($P = 0.324$), gender ($P = 0.546$)

PICU = pediatric intensive care unit

and operated side ($P = 0.805$). Positive cultures were obtained from 33% of the operated patients vs. 35% of the non-operated patients, while bacterial *Streptococcus pneumoniae* DNA PCR tests increased the overall yield to 44% and 58%, respectively. Since our center is a university hospital, 22% in the operated group and 54% in the non-operated group were referred to our department from other community hospitals. Computed tomography scans were performed in cases of severe clinical conditions and/or previous radiographic or ultrasonographic findings that correlated with complex pleural disease. CT scans were performed in 72% of the operated patients vs. 62% of the non-operated. Anamnestic reports revealed that 28% in the operated group and 31% in the non-operated group had suffered from chronic illnesses or repeated pneumonic episodes before their admission.

As the streptokinase washing protocol was begun in July 2007, characteristics of the stage II empyema patients with reference to the initiation time of this fibrinolytic treatment protocol are presented in Table 2. Notably, prior to July 2007, 23 patients with stage II empyema were registered, of whom 17 had undergone decortication surgery. After July 2007, 21 patients with stage II empyema were registered and only one required surgery.

MORTALITY AND MORBIDITY

All children in the study had complete recovery with full lung expansion according to chest X-ray. No disease sequelae were reported at clinical follow-up. No major adverse effects of streptokinase were noted, such as anaphylactoid reaction, arrhythmias, bleeding, polyneuropathy, or non-cardiogenic pulmonary edema. Minor adverse affects such as fever or shivering were observed in only a few patients but were hard to distinguish from typical empyema symptoms.

There were two cases of mortality in the stage I empyema group. Both were children with chronic illnesses: one with chromosome 21 trisomy and new onset of acute lymphocytic leukemia, and the other with cerebral palsy and acute respiratory insufficiency. Death was not attributed to empyema in either case.

Two cases in the stage II non-operative empyema group were excluded from statistical analyses. These were children with respiratory failure and prolonged mechanical ventilation in whom empyema developed late in their course of hospitalization.

STUDY OUTCOME MEASURES

- **Number of PICU admissions:** The proportion of pediatric empyema patients who were admitted to the PICU after the non-operative treatment was significantly smaller than in the operated cohort ($P = 0.0006$): Of the 26 non-operated patients, 8 were admitted to the PICU, i.e., less

Table 1. Clinical data of stage I and stage II pediatric empyema patients

	Treatment approach to stage II empyema			Stage I empyema
	Operative	Non-operative	P	
No. of patients	18	26 (2 excluded)	–	31
Chest drainage	6 (presurgical)	25	< 0.0001	1
Use of fibrinolytic agents	5 (unsuccessful)	16 (successful)	0.027	0
Age (yrs)	6.78 ± 4.21	5.29 ± 5.15	0.540	5.97 ± 5.33
Male	10 (56%)	12 (46%)	0.514	17 (55%)
Female	8 (44%)	14 (54%)	0.514	14 (45%)
Right-side disease	9 (50%)	12 (46%)	0.794	12 (39%)
Left-side disease	9 (50%)	14 (54%)	0.794	19 (61%)
Positive culture	6 (33%)	9 (35%)	0.891	0
Positive PCR	2 (11%)	6 (23%)	0.310	0
Referred from community hospitals	4 (22%)	14 (54%)	0.034	3 (10%)
CT scan	13 (72%)	16 (62%)	0.491	2 (6.5%)
Chronic illnesses	5 (28%)	8 (31%)	0.831	12 (39%)

PCR = polymerase chain reaction

Table 2. Clinical data of stage II pediatric empyema patients with reference to when the fibrinolytic treatment protocol was begun

	Before July 2007	After July 2007	P
No. of treated patients	23	21	
No. of operated patients	17 (74%)	1 (5%)	< 0.0001
No. of non-operated patients	6 (26%)	20 (95%)	< 0.0001
Use of fibrinolytic agents	7 (30%)	14 (67%)	0.141
Age (yrs)	5.83 ± 3.95	6.03 ± 5.65	0.483
Male	14 (61%)	8 (38%)	0.123
Female	9 (39%)	13 (62%)	0.123
Right-side disease	11 (48%)	10 (48%)	1
Left-side disease	12 (52%)	11 (52%)	1
Positive culture	9 (39%)	6 (29%)	0.485
Positive PCR	4 (17%)	4 (19%)	0.863
Referred from community hospitals	6 (26%)	12 (57%)	0.037
CT scan	17 (74%)	12 (57%)	0.235
Chronic illnesses	8 (35%)	4 (19%)	0.234

than 31%, whereas of the 18 operated pediatric patients, 15 were admitted to the PICU, over 83%.

- **Duration of PICU stay:** The duration of PICU stay among pediatric empyema patients who were admitted to the PICU following the conservative care was significantly shorter compared to the operated patients ($1.04 ± 1.9$ vs. $2.56 ± 1.92$ days, respectively, $P = 0.0148$).
- **Duration of hospitalization:** The duration of hospitalization was comparable ($P = 0.301$) between the group of pediatric

PCR = polymerase chain reaction

patients treated non-operatively (11.70 ± 5.74 days) and those treated with the operative approach (13.33 ± 3.69 days).

DISCUSSION

The major finding of the present study was that the non-operative streptokinase-based treatment protocol for pediatric empyema proved successful, as reflected by the reduced number of PICU admissions, shorter duration of PICU stay, and shorter overall hospitalization stay. Most importantly, the non-operative approach in the current study did not compromise the overall goal of full recovery from empyema. These advantages attest to the clinical benefits of the current intrapleural streptokinase washing protocol, which is based on the administration of 20,000 or 10,000 U/kg daily over 3 consecutive days, depending on the patient's age.

The most effective treatment approach for pediatric empyema is still controversial, however. The operative approach, which is supported because of the shorter hospitalization, includes VATS or open thoracotomy with decortication. Of these, the less invasive VATS is preferred owing to reports of its safety, efficiency, shorter hospitalization and earlier recovery [3,12,17,18]. However, Gates et al. [12] reported that non-operative approaches resulted in shorter hospitalization and intensive care unit stay. In the same line, recent evidence suggests that VATS has no therapeutic or recovery advantages over the non-operative approach of fibrinolysis for the treatment of pediatric empyema, and that fibrinolysis may pose less risk of acute clinical deterioration and should be the first-line therapy for children with empyema [4]. In keeping with Gates' findings, the operated pediatric empyema patients in the current study were not hospitalized for shorter periods than were the non-operated patients; in fact, the non-operated cohort demonstrated a tendency of an even shorter recuperation period.

The fibrinolytic agent that we chose for the non-operative treatment was streptokinase, based on our vast experience with this agent in the adult population where there were relatively few adverse effects and good success rates, in keeping with the literature [12,15,16]. The current study protocol was based, with some modifications, on several prior clinical work, namely: a) administering streptokinase as the fibrinolytic agent, 20,000 U/kg for 3 consecutive days; b) reducing the administration of the fibrinolytic agent in pediatric patients to only once a day; c) using X-ray imaging as part of the daily clinical follow-up for the fibrinolytic pediatric empyema patients; and d) evaluating the treatment's efficacy daily within a time frame of 3 days, after which, in case of ineffective clinical outcome, surgery was performed. We believe that the relatively unsuccessful results of fibrinolysis prior to

July 2007 were mostly due to lower agent concentration or insufficient number of pleural washings.

Regarding intrapleural fibrinolytics, the British Thoracic Society guidelines for the management of pleural infection in children stress that intrapleural fibrinolytics shorten hospital stay and are recommended for any complicated parapneumonic effusion or empyema; and despite the fact that urokinase is the only agent to have been studied in a randomized controlled trial in children it has not demonstrated greater efficacy compared to streptokinase [19]. As to referring pediatric patients to surgery, the British Thoracic Society emphasizes that failure of chest tube drainage, antibiotics and fibrinolytics should prompt early discussion with a thoracic surgeon, and patients should be considered for surgical treatment if they have persisting sepsis in association with a persistent pleural collection despite chest tube drainage and antibiotics [19].

The psychological impact on children during their stay in the PICU is dramatic. Therefore, the psychological aspect should be debated when selecting a treatment approach that affects these PICU-related outcomes, especially as less invasiveness correlates directly with decreased psychological sequelae [20]. Rees et al. [21] compared PICU-discharged children to matched ward-discharged children, and reported that one in every five children in the former group developed clinically significant post-traumatic stress levels, which was corroborated at 3 and 8 months after PICU discharge [22,23]. Importantly, none in the comparison group in the study by Rees et al. [21] demonstrated PTSD. Moreover, the PICU-discharged children exhibited increased rates of avoidance and rated themselves as having a high degree of fear for life. Jones and collaborators [22] reported that more than a quarter of the 1455 children assessed 6 months after PICU discharge had mild emotional impairment. Furthermore, as empyema is seen more often in older children than in infants, and as the levels of PTSD symptoms are reported more by older children [24], it can be deduced that the population of older children who are at risk should be more rigorously screened for non-operative empyema treatment before surgery.

Additional benefits, pertinent to health facilities, resulting from the decrease in the number of PICU admissions and the reduced stay in the PICU among the non-operated pediatric empyema patients, are the lighter ICU workload, which directly affects both caregivers and patients [25], and reduced treatment costs [4,12].

Several limitations of the current study should be acknowledged. First, our findings are derived from a retrospective analysis; prospective studies may reveal additional characteristics of non-invasive empyema treatment. Second, the groups in the current study included relatively small numbers of empyema patients; larger samples may yield more generalizable results.

VATS = video-assisted thoracic surgery

PTSD = post-traumatic stress disorder

Finally, the post-treatment follow-up was relatively short; longer periods may allow a more thorough delineation of the patients' recuperation process, both clinically and radiologically.

The main conclusion of the current study was that the non-operative intrapleural streptokinase washing protocol for pediatric empyema treatment is both safe and effective in terms of full recuperation, fewer PICU admissions and shorter PICU stays, as well as comparable hospitalization durations compared to the operated group. While physicians should be aware that fibrinolytic treatments may not always be successful, in which case conversion to the surgical approach is needed, our findings support the view that streptokinase-based management should be considered as a first-line therapy for pediatric empyema.

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