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Intrapleural Fibrinolytics in Children and Adolescence – Low Adherence to Published Guidelines and Influence of Internal Standards

***Roland Haase*[1,2]*; *Jan Baier*[2]; *Stefan Eisenmann*[2]**

[1]*Hospital St. Elisabeth & St. Barbara, Mauer St. 5, 06110 Halle, Germany.*

[2]*University hospital, Martin-Luther-University Halle; 06097 Halle, Germany.*

***Corresponding Author(s): Roland Haase**

Hospital St. Elisabeth & St. Barbara, Mauer St. 5, 06110 Halle, Germany.

Tel: 0345-213-4520, Fax: 0345-213-4222;

Email: r.haase@krankenhaus-halle-saale.de

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Abstract

Background: Parapneumonic Pleural Effusions including Pleural Empyema (PPE/PE) are rare complications of respiratory infections in children. Chest tube drainage and intrapleural fibrinolytics are used since more than ten years mainly in order to avoid surgery. Athough guidelines regarding the use of fibrinolytics exist, clinical practice is often different and literature is confusing. Internal standards are intended to support the implementation of guidelines according to local circumstances.

Methods: Guideline adherence in pediatric patients treated for PPE/PE before and after implementation of an internal guideline regarding the use of fibrinolytics was analyzed retrospectively.

Results: 20 patients (10 girls, 10 boys) were included. Diagnostic imaging consisted of chest radiography, CT and ultrasound in all patients. 19 (95%) patients received Urokinase and 1 patient (5%) r-tPA. Clinical and radiological improvement at discharge was noted in all patients. 20 of 20 (100%) patients had residual findings on chest. No patient required surgery. We found an improved guideline-adherence regarding dose and dose interval and less treatment days with fibrinolytics after standard implementation.

Conclusions: The implementation of an internal standard for treatment of PPE/PE with intrapleural Urokinase improved guideline adherence, but an evidence-based diagnostic and therapeutic algorithm for treating this serious complication is urgently required.

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Introduction

Respiratory infections remain a major cause of morbidity and hospitalization in children [1,2]. In contrast to the low incidence in ambulatory treated pneumonias, parapneumonic pleural effusions including pleural empyema (PPE/PE) are not rare in hospitalized children with pneumonia [3-5]. About 0.6-2% of children with community acquired pneumonia develop PPE/PE [6]. In a study from Poland, the proportion of hospitalized children with Pneumonia related PPE/PE increased from 5.4% in 2002 to 18.8% in 2013 [7]. Further studies also suggest an increasing incidence of PPE/PE [7-11]. The worldwide predominant causative pathogen is Streptococcus pneumonia, accounting for about 50% of cases, followed by Streptococcus pyogenes and Staphylococcus aureus [8,12-17]. Standard therapy includes broad-spectrum antibiotics, thoracentesis, chest tube drainage and –more as rescue - surgical intervention. Intrapleural fibrinolytics in addition to chest tube drainage may avoid surgery by breaking fibrin strands and membranes. Several publications including meta-analyses regarding the role of fibrinolytics show contradictory results [6,18-22]. However, intrapleural fibrinolytics in addition to chest drain and antibiotics are recommended by a guideline of the British Thoracic Society (BTS) from 2005 and a more recent German AWMF guideline [4,14]. The BTS recommendation, which contains information on dose, dose intervals and duration of fibrinolytic treatment, was the basis of a 2014 implemented internal guideline for the use of intrapleural fibrinolytics.

In this retrospective analysis, we describe our experience in the treatment of pediatric PPE/PE with fibrinolytics and physician adherence on external and internal guidelines for treatment of PPE/PE.

Materials and methods

Patients

The clinical course of 20 pediatric patients treated for PPE/PE between 1/2008 and 8/2020 by pleural drainage and fibrinolytics has been reviewed retrospectively. Patients were identified by screening of the electronic patient files. Data were extracted by additional chart review. The following data were recorded: sex, age at admission, symptoms at discharge, length of stay, choice, dose, dose interval and length of administration of fibrinolytics and need for surgery. The patients were divided into two groups: children treated before (Group-A, 2008-2014) and after (Group-B, 2015-2020 internal guideline implementation). We compared both groups regarding treatment results and guideline adherence (see below). Treatment was correct if it followed the BTS (Group-A) or our internal (Group-B) guideline.

Treatment algorithm

At our institution, a local treatment algorithm regarding the use of Urokinase for treatment of PPE/PE was implemented in 2014. This standard contains indication, dose, dose intervals and dwelling time according to the BTS guideline. The two guidelines do not differ regarding the use of Urokinase. Indications for intrapleural fibrinolysis are failure of conservative treatment and proof of loculated pleural fluid with strands, membranes and thickened pleura.

Following the BTS guideline Urokinase should be given twice daily for 3 days (40 000 units in 40 ml 0.9% saline per dose for children weighing ≥10 kg, and 10 000 units in 10 ml 0.9% saline per dose for children weighing <10 kg) [4,14]. The recommended dwelling time is 4 hours. Shortening of treatment was possible in case of artificial drain loss. Failure of conservative treatment was defined as worsening of radiological, laboratory and/ or clinical findings despite proper antibiotic treatment. Surgery, including Video Assisted Thoracoscopic Surgery (VATS) was discussed with pediatric surgeons in case of persisting sepsis or organized empyema and failure of chest tube drainage, antibiotics, and fibrinolytics, respectively.

PPE/PE

The diagnosis of PPE/PE based on patients history (fever, cough, failure of antibiotic treatment) clinical symptoms (respiratory distress, fever), laboratory results (elevated infection parameters) and radiological (Ultrasound, X-ray) appearance. The BTS as well as the internal guideline do not recommend a routine Chest-Computed Tomography (CT) before pleural drain insertion and administration of intrapleural fibrinolytics.

Response assessment

At our institution, radiographs are stored in a central radiological database. All X-rays were reviewed retrospectively. The maximal horizontal extent of pleural opacity was measured on anterior-posterior chest X-rays at start of treatment, after six fibrinolytic courses (or less in case of premature treatment termination) and at discharge and expressed as a percentage of the maximum diameter of the thorax. Treatment success was defined as resolution of symptoms and decrease of thickness of pleural opacity at discharge.

Technique

Insertion of chest drain and administration of local fibrinolytics was carried out in patients with proven PPE/PE and failure of conservative therapy. The insertion was done under procedural sedation at the pediatric intensive care unit with ultrasonographic guidance following standard methods. For insertion, the forth intercostal space in the posterior axillar line was preferred. Procedure associated complications did not occur. For fibrinolytic therapy Urokinase or r-tPA (one case) were diluted with normal saline (1000 IE/ ml for Urokinase or 0.2 mg/ml for r-tPA) and administered into the pleural space through the pleural drain. After instillation, the tube was clamped for 4 hours. Then the drain was unclamped and put under suction. Removal of chest tube was discussed if the daily drainage output was lower than 30 ml per day.

Statistics

Results were summarized using descriptive statistics. Categorical variables were compared using the Chi-square test or the Fisher's exact test, median levels by non-parametric tests and means by the paired sample t–test. P-values < 0.05 were considered statistically significant.

Results

20 patients (10 girls, 10 boys; median age 2.5 years) with PPE/PE were included. The median age was 2.5 (range 1.0 -16.7) years, the median length of stay 21 (range 14 - 48) days. No patient had a history of important medical problems. The empyema was right-sided in 7 (35%) and left-sided in 13 (65%) patients. 16 (80%) patients were referred from other hospitals because of increasing respiratory distress due to pleural effusions and 4 (20%) patients from their ambulatory pediatrician because of pneumonia. 19 (95%) patients received Urokinase and 1 patient (5%) r-tPA. Streptococcus pneumonia was found

in 5 (25%) patients, other bacteria in 5 (25%) (2 Streptococcus pyogenes, 1 Streptococcus constellatus, 1 Streptococcus sanguis, 1 Staphylococcus epidermidis), Influenza virus A or B in 2 and no organism in 8 (40%) patients. The length of antibiotic therapy prior to drainage varied between 0 and 24 (median 4) days. The pleural drain was inserted between 0 and 14 (median 0.5) days after admission and in all patients with ultrasonographic guidance.

Diagnostic imaging consisted of chest radiography, CT and ultrasound in all patients. Ultrasound was also used for staging of PPE/PE. Comparing Group–A and Group-B we found an improved guideline-adherence regarding dose and dose interval and less treatment days (Table 1). Fibrinolytics were given for a median of six (range 2–11) days. Two (10%) patients were treated less than three days and 13 (65%) six or more days. One (5%) patient received exact six doses. The dose interval was 8 hours in eight (40%) and 12 hours in 12 (60%) patients, respectively. Chest-radiographies showed mean opacities of 41.3% (before first), 40.5% after six fibrinolytic courses and 7.1% at discharge (Table 1, Figure 1). Clinical and radiological improvement at discharge was noted in all patients. 20 of 20 (100%) patients had residual findings on chest-radiographies (increased pleural thickness, pleural scares or unilateral increased opacity). No patient required surgery.

Systemic fibrinolysis or bleeding did not occur. Three (10%) patients suffered from chest pain especially during administration of Urokinase and two patients developed a pneumothorax after drain removal. Pleural drainage was necessary in both patients.

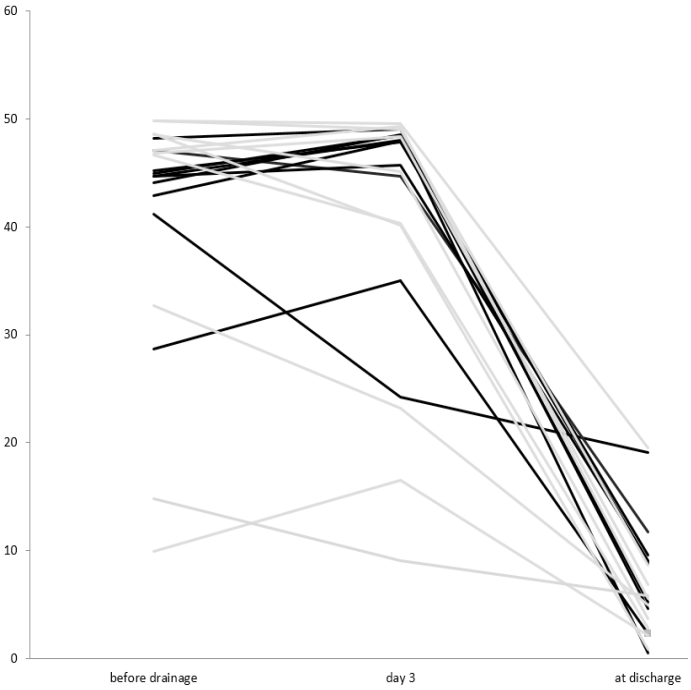

Figure 1: Response to treatment. The reduction of the maximal horizontal extent of pleural opacity on anterior-posterior chest X-rays at start of treatment, after six doses of fibrinolytics and at discharge are expressed as percentage of the maximum diameter of the thorax (Y-axis). Each line represents one patient. There was no difference between Group-A and B. Black, Group-A; grey, Group-B.

Table 1: Results of treatment and adherence to guidelines. According to the BTS guideline one patient who received r-tPA was counted as correct regarding choice of fibrinolytic, dose and dose interval. The maximal horizontal extent of pleural opacity was measured on anterior-posterior chest X-rays at start of treatment, after six fibrinolytic courses (or less in case of premature treatment termination) and at discharge and expressed as a percentage of the maximum diameter of the thorax.

	Group-A	Group-B	p - value
n	10	10	n.d.
chocice of fibrinolytic correct	10	10	n.d.
dose correct	5	10	0.08
dose interval correct	3	9	0.05
days of fibrinolytics	9	6	> 0.05
opacity (%) before drainage, mean	43,2	39,5	> 0.05
opacity (%) day 3, mean	43,9	37,1	> 0.05
opacity (%) at discharge, mean	8	6,1	> 0.05
length of stay (d), median	19	21	> 0.05

Discussion

About 70% of all PPE/PE recover with conservative management, which is defined as treatment with antibiotics alone or with antibiotics and simple drainage [4, 14]. Accepted criteria for intrapleural fibrinolytics are missing clinical improvement with persistent fever after 48 – 72 hours conservative treatment, deterioration of clinical symptoms or laboratory values and detection of loculated pleural fluid with strands, membranes and thickened pleura. Fibrinolytics might solve fibrin adhesions and strands as well as open lymph pores to re-enable pleural fluid circulation. Three fibrinolytics (Urokinase, Streptokinase and r-tPA) have been described for pleural instillation [23-26], but a therapeutic advantage of one of them compared to the others has not been proven. In contrast to the BTS guideline, the newer AWMF guideline does not recommend Streptokinase, probably because of potentially dangerous allergic reactions. Studies regarding fibrinolytics are difficult to compare because of differences in the choice of fibrinolytic, dose, dilution, dwell time and length of treatment. In contrast to single studies meta-analyses regarding the treatment of PPE/PE do not confirm a benefit of intrapleural fibrinolytics compared to conservative management [18,20,22].

In this retrospective analysis we report our experience with the use of intrapleural fibrinolytics in children with PPE/PE. Corresponding to other authors, we found an excellent clinical outcome [10,27]. All patients recovered without clinical symptoms. Also corresponding to the literature radiographies at discharge showed persistence of radiological abnormalities. Such findings without clinical symptoms and normal lung function should not lead to further diagnostic or therapeutic interventions, but medical attendance by a pediatrician with experience in pediatric pulmonology is necessary.

According to the guidelines, physicians used chest radiographies and ultrasound for diagnosis and ultrasonographic guidance for insertion of chest tube. Although mostly not necessary, all patients received a chest-CT before thoracostomy. As shown in a study by Hafen this approach is standard in about 25% of European pediatric centers [28]. Chest ultrasound is superior to

CT at revealing pleural septa and loculations [29,30]. Chest-CT may be helpful in diagnosis of the cause of pleural effusions and delimitation of a suspected lung abscess in pleural infection. However, in most patients chest sonography provides sufficient information so that CT associated risks (radiation, transport and possible procedural sedation) are not justified. Ultrasonographic guidance of pleural puncture leads to less complications like pneumothorax or bleeding [31].

The length of stay (calculated from the initial admission) was relatively long. The majority of patients came from other hospitals because of failure of antibiotic treatment, persistent or increasing PPE/PE. Therefore, in most cases we were unable to determine the choice and duration of initial antibiotic and supportive treatment as well as the time of pleural drainage. However, in 13 (65%) patients chest drain insertion and intrapleural fibrinolytics started within 3 days after admission to our hospital.

The BTS and our internal guidelines clearly define doses, dose intervals, dwelling time and treatment duration. Surprisingly, especially in Group-A, we found a low adherence regarding the dose, dose interval and treatment duration. Pediatricians usually calculate doses based on body weight or body surface area. Possibly, therefore many pediatricians preferred the administration of 1000 IU Urokinase per kilogram body weight and not the recommended two-stage regimen. The implementation of the internal guideline significantly improved the prescribing behavior. In addition, clinical and radiological improvement as well as a decrease of draining volume will take time. This could explain why doctors, obviously tended to prolong treatment.

Another reason for the disappointing result in Group-A might be the "lack of mutual consensus among the four countries regarding the management of pediatric parapneumonic effusion" as described in a recent study including leading pediatric pulmonologist in Austria, France, Germany and Switzerland [28]. Physicians find a variety of conflicting publications and recommendations on the role of fibrinolytics and surgery [32]. Low evidence and contradicting studies lead to different therapeutic approaches even in the same institution.

Corresponding to the low rate of surgical intervention in the pediatric literature none of our patient required surgery [33]. Surgical methods include video-assisted thoracoscopic surgery (VATS), mini-thoracotomy and decortication by open surgery. However, although surgery is mostly reserved for patients with failure of antibiotics, chest drain and fibrinolytics early consultation of a pediatric surgeon is strongly recommended.

Conclusions

Our experiences indicate that intrapleural fibrinolytics are feasible and safe in children. The introduction of an internal guideline for treatment of PPE/PE on the pediatric intensive care ward improved the adherence on the guideline without loss of quality. Because the literature shows a lack of consensus on optimal management of PPE/PE, internal guidelines are necessary and helpful. However, in order to offer the best possible treatment and to prevent long-term consequences we urgently require an evidence-based diagnostic and therapeutic algorithm for treating this serious complication.

Conflicts of Interest

The authors declare no conflict of interest.

The work was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were not applicable.

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