Original Article

Fibrinolysis versus thoracoscopy: Comparison of results in empyema management in the child

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Abstract:

OBJECTIVE: The objective of this study is to compare the outcome of treatment with drainage and urokinase (UK) versus thoracoscopy (TS) in pleural empyema secondary to complicated pneumonia.

METHODS: This was a retrospective study of patients with complicated parapneumonic effusions between 2008 and 2019 treated with UK or TS. Epidemiological and evolutionary data compared days of fever, antibiotic, pre- and postprocedure stay, time to radiological resolution, and complications. The results were expressed as medians and the comparisons were made by the Mann–Whitney U-test.

RESULTS: Of 143 patients with NC, 46 were empyemas (26 men), 25 were treated with TS, and 10 were treated with UK. The remaining 11 received combined treatment, being excluded from the study. There were no significant differences between TS versus UK in age (median 4 vs. 3 years), days of fever before the procedure (4 vs. 2) and after (2 vs. 2), days of antibiotic treatment before the procedure (4 vs. 4), overall hospital stay (15 vs. 13 days), and months until radiological normalization (2 vs. 2). The complications related to the therapy were scarce in both groups and had no impact on evolution. Patients with TS had a longer preprocedural stay (4 vs. 1; $P < 0.001$) and required fewer days of subsequent antibiotic after procedure (8 vs. 11; $P = 0.03$), and a shorter overall antibiotic treatment time (11 vs. 16; $P = 0.03$). They also had a shorter post-TS stay (9 vs. 12 days), although this difference did not become significant ($P = 0.09$).

CONCLUSIONS: In our experience, the results obtained with both procedures are quite similar, although patients undergoing TS had a better evolution (fewer days of antibiotic and a tendency to less hospitalization), despite having been performed *a priori* in more evolved patients.

Keywords:

Empyema, fibrinolytics therapy, thoracoscopy, urokinase

Parapneumonic pleural effusion is the most frequent complication of bacterial pneumonia in childhood. In some series, up to 30%–40% of pneumonias requiring hospitalization are complicated by pleural effusion and 0.6%–2% progress to empyema.[1,2] The incidence of parapneumonic effusion in the pediatric population is increasing worldwide.[3,4] In Spain, an increase from 1.7 to 8.5 cases/100,000 children has been documented since the late 1990s.[5]

The reasons for this significant increase are unknown, but possibilities include the increase in bacterial resistance, climatic changes, introduction of the pneumococcal vaccine, and prescription of antibiotics from primary care.[6]

The effusion may progress to empyema in three stages: [4]

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- The first stage describes an inflammatory, clear-appearing, low-viscosity, and sterile exudate that usually resolves with antibiotic treatment with or without simple drainage
- The second stage (fibrinous-purulent) is a consequence of leukocyte migration and formation of fibrin deposits in the pleural space. This causes the loculation of liquid and viscous pus
- In the third stage, the formation of a thick membrane covering the visceral pleura (organized empyema) occurs, causing a rigid "shell," which limits lung expansion and ventilation.[7,8]

This pathology usually occurs in healthy patients, although it can also be the consequence of thoracic trauma, inhalation of a foreign body, immunodeficiency states such as hypogammaglobulinemia, and immunosuppression after chemotherapy, corticosteroid treatment, or malnutrition.[7]

To improve the evolution of these patients, different strategies have been implemented to treat empyema: thoracic drainage with intrapleural instillation of fibrinolytic urokinase (UK), thoracoscopy (TS), and thoracotomy with decortication (TT). However, there is great variability in clinical practice in the management of empyema in children. The ideal initial treatment is controversial.[8] Some authors advocate the early use of TS, while others prefer the initial use of thoracic drainage with fibrinolytics.

We therefore propose to analyze our experience in a pediatric surgery unit in the management of empyema secondary to complicated pneumonia (CP), comparing both treatment strategies.

Methods

A retrospective observational study of pediatric patients (aged 0–14 years) with complicated parapneumonic effusions attended by pediatric surgeons at a tertiary referral hospital between 2008 and 2019 was performed. The diagnosis of pleural effusion was established by physical examination, plain chest X-ray, and ultrasound. The latter was used to classify the effusion as simple (free fluid without septa) or complicated (the presence of septa, fibrin, and detritus, adhesions to pleura, pachypleuritis, or organized and encapsulated "honeycombed" effusion). Other complementary tests included microbiological and biochemical analyses of pleural fluid and, in some cases, computed tomography.

Patients with complicated effusion, who required treatment with UK or with TS, were selected, excluding those resolved by antibiotherapy ± thoracic drainage. To analyze the possible differences between those treated only with UK or TS without any other added treatment, patients who received combined treatment (TS + UK) were also excluded from the study. There was no prior criterion for the selection of the therapeutic modality, and patients were treated with UK or TS according to the preference of the team in charge.

In the UK group, chest drainage was placed in the operating room under general anesthesia or in the pediatric intensive care unit with sedation, under sterile conditions, and with tubes of caliber from 12 to 14 Fr in infants and up to 20–22 Fr in adolescent patients. Insertions were performed between the fifth and sixth intercostal space, in the midaxillary line, and a continuous negative pressure of 15–20 cmH2O was subsequently applied. The position of the drainage tube was verified by chest radiography.

Fibrinolytic instillation was started after drain placement or the following day and consisted of 3 daily boluses of a 1000 intrapleural units (IU)/ml dilution of UK in saline at a dose of 10,000 IU/kg/day.

After administration of the fibrinolytic, the drainage was clamped for 4 h and unclamped for the following 4 h, during which the drainage was maintained under suction. Patients were closely monitored from the start of treatment, and adverse events were recorded and frequent postural changes and ambulation were prescribed, if possible, in addition to analgesia.

Chest drainage was removed when respiratory signs and symptoms had significantly improved, drainage was minimal (<20–40 ml/24 h), they were afebrile in the past 48–72 h, and there were no radiological signs suggesting persistence of empyema.

TS was performed under general anesthesia with the patient placed in lateral decubitus on the healthy side. Selective bronchial intubation was not performed but pneumothorax with low CO_2 pressures (4–6 mmHg). Two or three 5 mm trocars were used, the first one being placed in the area marked by ultrasound where there was more fluid. Through this trocar, the 0° optic was introduced. The visual control of the pleural space allowed the placement of the second trocar or a third one according to the needs. Debridement of the septa was performed with an aspirator or forceps. The greatest possible amount of fibrin deposited in both the parietal and visceral pleura was removed, and the pleural cavity was cleaned with abundant physiological saline and suction, avoiding excessively high intrathoracic pressures that could alter ventilation. One or two chest drains were left in place, which were

removed when they met the same criteria as in the UK group.

Failure of both treatments was considered when there was no clinical improvement (fever, respiratory symptoms, or pain) in 3–5 days of treatment and when poor drainage through the tube despite the persistence of empyema in imaging tests.

All the patients received analgesia after the procedure with metamizole every 6 h and a rescue therapy based on acetaminophen or ibuprofen, and exceptionally, some patients required some doses of tramadol.

Age, sex, empyema location, symptomatology and initial antibiotic treatment, specific etiology, analytic parameters, days of fever, antibiotic administration and pre- and postprocedural stay, time to radiological resolution and complication rate in each case were recorded. The complications considered were the presence of a significant air leak, bleeding after the procedure, severe bronchospasm, and anaphylaxis after administration of UK.

The results were expressed as proportions and medians with interquartile range (IQR); comparisons between both treatment groups with nonnormal distribution were performed by Fisher's exact test and Mann–Whitney *U*-test, with an accepted significance level of $P < 0.05$. The SPSS 20.0 program for Windows was used for the statistical analysis of the data (The SPSS 20.0 program for Windows, SPSS Inc., Chicago, IL).

Results

Of the 143 patients with pleural effusion associated with pneumonia evaluated during the study period, 46 were empyema, of which 11 cases that received combined treatment (UK + TS) were excluded from the study. Of the 35 patients finally analyzed, 25 were treated with TS and 10 with drainage and fibrinolytics.

Our trend in terms of the therapeutic approach employed over these years is shown in Figure 1.

Of the total number of patients, 18 were male and 17 female, with a median age of 4 years (IQR: 2–6), with no significant differences between the two groups in terms of age and sex. There were also no differences in the location of the parapneumonic effusion, which was predominantly right sided (56.3%).

The groups were also homogeneous in terms of clinical presentation, which was very similar in all patients: 96% of cases debuted with fever and respiratory distress and 8% with abdominal pain. There were no differences in

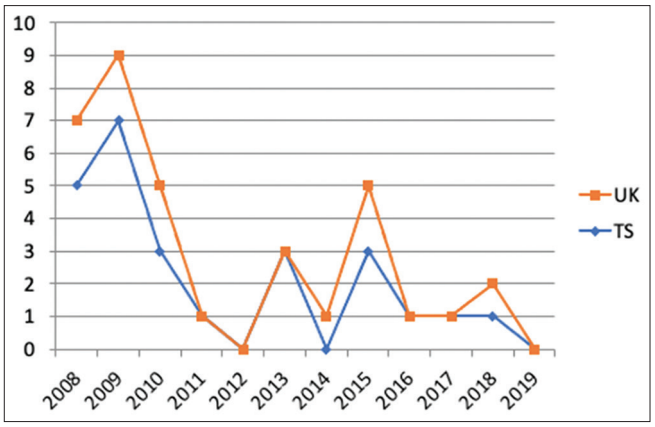

Figure 1: Trend in the therapeutic approach used in our series between 2008 and 2009

the duration of fever before treatment with TS or UK (4, IQR: 4, vs. 2, IQR: 5; p: not statistically significant [NS]), nor in the days of fever after treatment, with a median of 2 days in both groups.

Hundred percent of patients were receiving empirical antibiotic treatment at diagnosis (80% cefotaxime, 13% ampicillin, and 6% amoxicillin-clavulanic acid). This treatment and its length was adjusted according to microbiological diagnosis and/or clinical evolution.

The median duration of preprocedural antibiotic treatment, including outpatient treatment when prescribed, was 4 days (IQR 2) in the TS group and 4 days (IQR 3.25) in the UK group, with no significant difference between the two ($P = 0.31$).

The days of antibiotic therapy after the procedures were 8 days in the TS group and 11 days in the UK group ($P = 0.03$). The median duration of antibiotic treatment in total was 11 days (IQR 8) for patients treated with TS and 16 days for the UK group (IQR 6) ($P = 0.03$).

A microbiological diagnosis was reached in 60% of cases, with 85% Pneumococci, 10% viruses, and 5% Staphylococci. The results in each group are shown in Figure 2.

Patients were admitted for a total (mean) of 15 days (IQR 10) in the TS group and 13 days in the UK group (IQR 3.25) ($P = 0.76$). Although this difference was not significant, it did reach statistical significance for the preprocedural stay, which was longer in the TS group (4 days, IQR 3.5, vs. 1.5 days, IQR 1; $P < 0.001$); conversely, their postprocedural stay was shorter (9 days, IQR: 7, vs. 12 days IQR: 5), close to significance ($P = 0.09$).

According to the treatment-related complications, none of our patients suffered anaphylaxis after UK administration. We did not find any bronchopleural

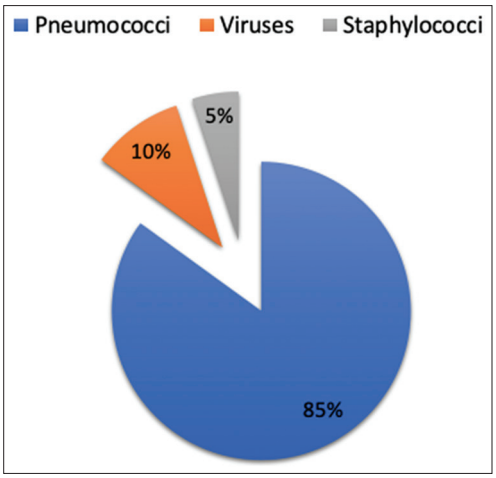

Figure 2: Microbiological diagnosis found in our series

fistula, prolonged air leak, or lung collapse after any of the procedures. One patient presented with post-TS bleeding with a decrease of more than two hemoglobin points requiring transfusion but not reoperation. None of the patients treated with TS required reconversion to TT.

There were also no significant differences in the time to radiological normalization, which was 2 months in both groups.

Of the 11 patients excluded because they had received combined treatment, five were those who required UK after having undergone TS and six those who required TS after having been prescribed UK (treatment failure rate with TS was 16% and 29% in those treated with initial UK). No significant differences were found (p: NS) in the treatment failure rate (16% in TS and 29% in UK).

Discussion

CP can be resolved with antibiotics and placement of thoracic drainage, but sometimes, the presence of fibrinoid material and loculations complicates the case. In these patients, the use of fibrinolytic substances, TS, or TC has been recommended to cut the pathophysiological phenomenon.

Nowadays, there are no standardized protocols or consensus regarding the treatment of empyema in pediatric patients. Despite being a pathology with an increasing incidence in recent years,[2,4] its incidence is still low, which makes it difficult to collect cases for further studies. In the retrospective analysis performed, a sample size of 46 patients with empyema over 11 years was obtained among a total of 143 patients with CP. It should be specified that the patients included in the study were those for whom the pediatric surgery service was consulted due to unfavorable evolution or nonresponse to initial treatment. Patients with empyema treated by the pediatric department, which would probably increase the number of cases, were not included in the study. It is also possible that this low number of cases is due to the high vaccination rate in our setting; this would be supported by the progressive decrease in the number of cases in our series, coinciding with the inclusion of the pneumococcal vaccine in the vaccination schedule.

In our series, we observed a median age of 4 years and a slightly higher incidence in males, results similar to those described in the literature; thus, in a study by van Loo *et al*.,[9] they obtained a median age of 4 years and an incidence in males of 57.1% (n of the study = 60 cases). Marhuenda *et al*.[10] found a mean age of 4.4 years and a slight predominance also in males, although these differences were not statistically significant.

As in our series, in both studies, the diagnosis was established by physical examination, radiography, and thoracic ultrasound, an examination that has been used to classify patients according to the stage of pneumonia.[4]

Regarding etiology, the results are also similar to those described by most authors: in the study by Griffith *et al*.,[4] most microbiological samples were negative (58%); however, in those positive, *Streptococcus pneumoniae* was the most frequently isolated germ. It was also the germ most frequently isolated by Marhuenda *et al*.[10] and Wolff Walker *et al*.[11] Some series showed a decrease in the incidence of this condition after the introduction of the pneumococcal conjugate vaccine in 2006.[12,13]

Regarding the therapeutic approach, there is no consensus in the literature either. The use of less invasive techniques such as TS surgery, described by Kern and Rodgers in 1993,[14] awakened a growing interest in surgery as an initial treatment and not only as a rescue therapy after medical treatment.

Its main advantages would be a decrease in the number of painful procedures, shorter hospital stay, earlier lung expansion, and a decrease in the pain associated with invasive procedures and in the anxiety of parents and children. This led to the early surgical approach to complicated pleural effusions being considered as the therapy of choice by some authors such as Doski *et al*.,[15] Hilliard *et al*.,[16] or Cohen *et al*.,[17] who demonstrated better results when compared to treatment with drainage and fibrinolytics.[17]

However, the role of surgery in the management of childhood empyema remains controversial,[18] and some studies, such as the one developed by Hamm and Light,[19] propose an initial approach based on the size of the effusion, ultrasound findings, pleural fluid analysis, and clinical evolution, moving from a more conservative

treatment to a more aggressive management in a stepwise manner.

It should be taken into account that the use of early pleural drainage facilitates the possibility of fibrinolytic treatment, which has been shown to be very effective.[20] Substances such as streptokinase, UK, and tissue plasminogen activator (alteplase) are used for this purpose. Few studies have been performed on children, although the use of these fibrinolytic substances appears to be a safe and well-tolerated procedure. UK is the best tolerated with fewer allergic and systemic reactions.[21,22] In fact, none of our patients suffered anaphylaxis after UK administration. Fibrinolytic therapy should be discontinued if ineffective, which may occur in very organized effusions, and should not be considered in patients with bronchopleural fistula or when the bubbling is seen in the pleural drainage tubes, which would suggest an air leak. Drainage tubes should be opened immediately if the child shows signs of clinical deterioration, such as increased shortness of breath or chest pain.[23]

A Spanish multicenter clinical trial compared the usefulness of UK with TS in 103 children with septated pleural effusion.[24] The results showed that the administration of UK was as effective as TS in the treatment of septated pleural empyema, with no difference in the length of hospital stay after the procedure. The failure rate of TS was 15% (16% in our series), and 10% in the UK-treated group (29% in our study).

Prospective randomized clinical trials by Sonnappa *et al*. in 2006[25] and St Peter *et al*.[26] in 2009 also compared TS and UK as initial treatments for empyema. Both are series of patients treated at a single center, with 60 patients included in the former and 36 in the latter. The designs are very similar, although the fibrinolytic used is different (UK in the Sonnappa *et al*. series and alteplase in the St. Peter *et al*. series). Neither of the two studies found significant differences between the two treatment groups in the main variable, postoperative hospitalization. Both also concluded that treatment with fibrinolytics is more economical than surgical treatment.

According to the results of Marhuenda *et al*.,[24] the treatment-related complications encountered in our study were minor, except for a case with significant bleeding in the TS group, requiring blood transfusion.

These results support the current recommendation of the American Pediatric Surgical Association to use fibrinolysis as the initial treatment in these patients, given its lower cost and greater simplicity, as it does not require surgical intervention.[25-27] The cost of TS is estimated to be higher than that of UK,[26] although some authors believe that early TS could be more effective and cost-saving.[28]

The review of our series, with the limitations inherent to a retrospective, single-center study, with a small sample size and a wide time window, shows that the results obtained with both procedures are quite similar, although the patients who underwent TS had a better evolution (fewer days of antibiotics and a tendency to a shorter hospital stay after the procedure), despite having been performed *a priori* in more evolved patients (longer hospital stay before the procedure).

Therefore, in line with the most recent literature, it seems sensible to recommend staged treatment, with the development of joint pediatric surgery and pediatric protocols that allow an early and appropriate approach to the severity of the condition and the early detection and treatment of possible complications or therapeutic failures. However, the debate is still open, and it is possible that the experience of each center will influence the choice of one of the two alternatives.

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Conflicts of interest
There are no conflicts of interest.

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