# VATS or Urokinase for Treatment of Empyema?

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**SUMMARY**

This randomized, multicenter clinical trial enrolled 103 children hospitalized with septated parapneumonic empyema (PPE) who were randomized to receive thoracoscopy ($n$=53) or urokinase ($n$=50). The main outcome variable was the length of hospital stay after treatment. The secondary outcomes were total length of hospital stay, number of days with the chest drain, number of days with fever, and treatment failures. No statistically significant differences were found between thoracoscopy and urokinase in the median postoperative stay (10 *vs* 9 days), median hospital stay (14 *vs* 13 days), or days febrile after treatment (4 *vs* 6 days). A second intervention was required in 15% of children in the thoracoscopy group versus 10% in the urokinase group ($P$ = 0.47). The authors concluded that drainage plus urokinase instillation is as effective as video-assisted thoracoscopic surgery as first-line treatment of septated PPE in children.

**COMMENTARIES**

***Evidence-based-medicine Viewpoint***

*Relevance:* Pediatricians often encounter pneumonia complicated by parapneumonic effusion (with or without empyema). Several reports [1-5] from Indian institutions confirm successful management with appropriate antibiotic therapy and intercostal drainage. However, some patients do not respond and require surgical procedures, including decortication. In recent years, medical management of complicated parapneumonic effusion/ empyema has been enhanced by intrapleural fibrinolytics. One of the earliest pediatric trials [6] conducted in our institution demonstrated that streptokinase instillation prevented the development of pleural thickening in children with multiloculated empyema; there were no benefits in other types of parapneumonic effusion. A 2010 systematic review of four pediatric trials [7] did not confirm definite benefit of fibrinolytics over placebo. Another systematic review [8] with 7 adult trials reported some benefit with fibrinolytic therapy (compared to placebo) in terms of reduced treatment failure, but no differences for duration of hospitalization.

Some institutions prefer surgical management as the primary approach to empyema, and video-assisted thoracoscopic surgery (VATS) has greatly reduced surgery-related morbidity [9]. It is interesting that reports from surgical units in India [10-12] suggest excellent outcomes with primary surgical management, and emphasize the importance of early intervention. In developed countries, empyema management (including intercostal drainage and fibrinolytic therapy) is often led by surgeons and such units report favorable results with conservative approaches also [13]. A recent meta-analysis of 10 trials [14] reported that intrapleural fibrinolytics reduced the need for surgery and duration of hospitalization. Sub-group analysis showed these benefits with urokinase but not streptokinase. However, fibrinolytic therapy did not reduce mortality. In contrast, a Cochrane review published in 2009 – but since withdrawn [15] – identified only one RCT comparing VATS and fibrinolytic therapy, concluding that VATS appeared superior for multi-loculated empyema. Against this backdrop, direct comparison between medical management (tube drainage with fibrinolytics) andVATS in children with empyema presented in a recent publication by Marhuenda, *et al*. [16] is timely and appropriate.

*Critical appraisal:* ***Table*** **I** summarizes the methodological aspects of the study. Although this was designed as a multi-centric study, the majority of patients were from the leading institution. Several methodological refinements enhance the trial quality. These include robust inclusion and exclusion criteria definitions, inclusion of only ultrasonographically confirmed multi-loculated empyema, and precise definitions of 'treatment failure'. Radiographic outcomes at follow-up were determined by specialists blinded to the clinical details. Standard protocols for medical (intercostal drainage and fibrinolytics) and surgical (VATS) management have been described. In general, the trial appears well-designed with

**TABLE I** CRITICAL APPRAISAL OF TRIAL METHODOLOGY

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|---|---|
| Generation of random sequence | Randomization sequence was generated by a computer program. Block randomization with variable block sizes was used. |
| Allocation concealment | Participants were allocated using a web-based system accessed by enrolling physicians after obtaining informed consent. |
| Blinding | There was no blinding of participants or outcome assessors. Radiologists reading the *X*-ray films at the 3-month follow-up visit were blinded. |
| Completeness of reporting | All randomized participants were included in the primary analysis. However 3-month follow up data was available in 79/103 participants with no clear explanation about the drop-outs. |
| Selectiveness of outcome reporting | All clinically relevant outcomes were included viz post-intervention duration of hospital stay (primary outcome), total duration of hospitalization, duration of intercostal drainage, treatment failure rate, complication rate, microbiologic analysis, and clinical as well as radiographic outcome at 3 months. |
| Similarity of groups at baseline | The two groups appear to be similar at baseline with respect to participant demographics, clinical features, and pleural fluid characteristics. |
| Sample size estimation | The authors' *a priori* sample size estimate could not be met within the duration of the trial. |
| Overall impression | Well designed trial with a low risk of bias. |

a low risk of bias. However the precise details of antibiotic choice and duration have not been given and these were probably not uniform across institutions.

*Extendibility:* The clinical problem presented in this trial (multiloculated empyema in children), choice of interventions, clinically relevant outcomes and overall trial design and procedures, make it appealing to extend the results to the Indian setting. However certain important differences should be noted. As in most studies from developed countries, the predominant pathogen isolated in the enrolled children was *S. pneumoniae*. In contrast, almost all Indian studies [1,2,4,5,10] report *Staphylococcus aureus* as the predominant pathogen. *S. aureus* empyema is associated with very thick pus that is not easy to drain, whereas *S. pneumoniae* pus is less viscous. Perhaps this is why guidelines in developed countries recommend relatively narrow chest tubes, whereas wider bore tubes are preferred in our setting.

Second, the investigators applied negative suction to the chest tube drainage; this tends to enhance pleural drainage and also helps to keep the adjacent lung expanded. Negative suction is not routinely practiced in our country, perhaps due to practical/logistic challenges. As in most western settings, the investigators chose to use urokinase, whereas Indian experience is mostly limited to streptokinase. The latter is reportedly associated with a greater frequency of immunological reactions [17]; however the clinical efficacy *versus* urokinase or alteplase has not been evaluated.

The trial investigators attempted to identify predictors of treatment failure but did not find any demographic, clinical or therapy-related features that correlated with clinical outcome. However, underlying malnutrition was not considered perhaps as it is not a significant problem in their setting, whereas clinical experience in India suggests that malnourished children have poorer clinical outcomes.

Finally, given that VATS may not be readily available in many Indian hospitals, its comparability with pleural drainage and fibrinolytic therapy (demonstrated in this trial), is encouraging for clinical settings across our country.

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### *Pediatric Pulmonologist's Viewpoint*

Empyema is a known complication of pneumonia; the frequency of this complication is not well documented. The earlier reports suggested a rate of less than 1% [18] while there have been other studies have reported occurrence of parapneumonic effusions in up to 12% [19]. The parapneumonic effusions may progress to fibrin deposition and formation of a thick cortex leading to lung entrapment; this requires a surgical decortication procedure.

In addition to the antibiotics, the pus has to be drained from the pleural space. This has been done using a tube thoracostomy or by thoracotomy; the former is the usual first step. However, a chest tube will not be able to drain

well in case of sepatations and loculations. The surgical procedures like VATS and thoracoscopic surgery may help drain the pus and remove septations and may facilitate an early discharge. Previously, pleurectomy decortication was performed in some children early in the course. However, the surgical facilities to undertake these procedures may not be available widely. In view of this limitation, it is worthwhile to explore if use of thrombolytics such as urokinase or streptokinase can facilitate the drainage of pleural collection even in presence of septations/loculations, reduce the duration of hospital stay and prevent the need of extensive surgical procedures like decortications.

The current study comparing intrapleural urokinase with VATS in a randomized controlled trial adds to evidence base required for comparing the two management strategies [16]. There was no significant difference in the primary and secondary outcomes except that the median duration of chest-tube placement was a day less in the VATS group. The adverse event rates were comparable.

As most of the resource-limited centers do not have an access to VATS, urokinase (or another thrombolytic like streptokinase) instillation may be the only option. The current practice also seems to prefer use of fibrinolytics [3,13]. Guidelines of the professional bodies also seem to favor use of intrapleural fibrinolytics over VATS in early management of children with empyema; VATS is recommended in case of failure of treatment or development of organized empyema [20,21]. However, various centers that have facilities for VATS may prefer to use the same over fibrinolytics. In the Indian setting, the choice of VATS is likely to be more expensive than use of fibrinolytics.

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### *Pediatric Surgeon's Viewpoint*

This paper describes the results of comparison of the two most common procedures used for management of empyema. While it is a properly conducted randomized controlled trial, it has not incorporated some useful practical points. Urokinase as an injection has been used in various doses in various studies. The exact dose is not yet defined and depends on the viscosity of the fibrinopurulent exudate. It also mandates the monitoring of coagulation profile at regular intervals. Urokinase is preferred in loculated empyema, where the pig tail catheter may be placed under ultrasonographic guidance. It is less painful as smaller bore chest tubes may be used. The blood loss is not much as the exudate is removed in various steps and not in one go. It allows for healing and debridement at the same time which is an important aspect of good wound healing. The chest expands slowly with physiotherapy and there are less chances of recurrence.

VATS is definitely more expensive and requires an operation theater setting; it is usually done as a planned procedure and thus delays the institution of therapy. Also it is done under general anaesthesia which subjects the underlying diseased lung to anaesthetic agents and ventilator. The patient is subjected to additional morbidity of post-operative period. Though most studies comparing these two modalities find no evident difference between the two (apart from the expenses), in practice fibrinolysis has less risk of acute clinical deterioration and should be the first-line therapy for children with empyema. In cases where it fails with persistent symptoms or loculations after one week, VATS definitely has a role. In cases that are presenting during the last phase of the fibrinopurulent stage and the facility for VATS is available in emergency, VATS may be tried as the first option to prevent the empyema from going into the organizing stage. In today's era of early diagnosis, very few patients should be subjected to an open decortication procedure.

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