

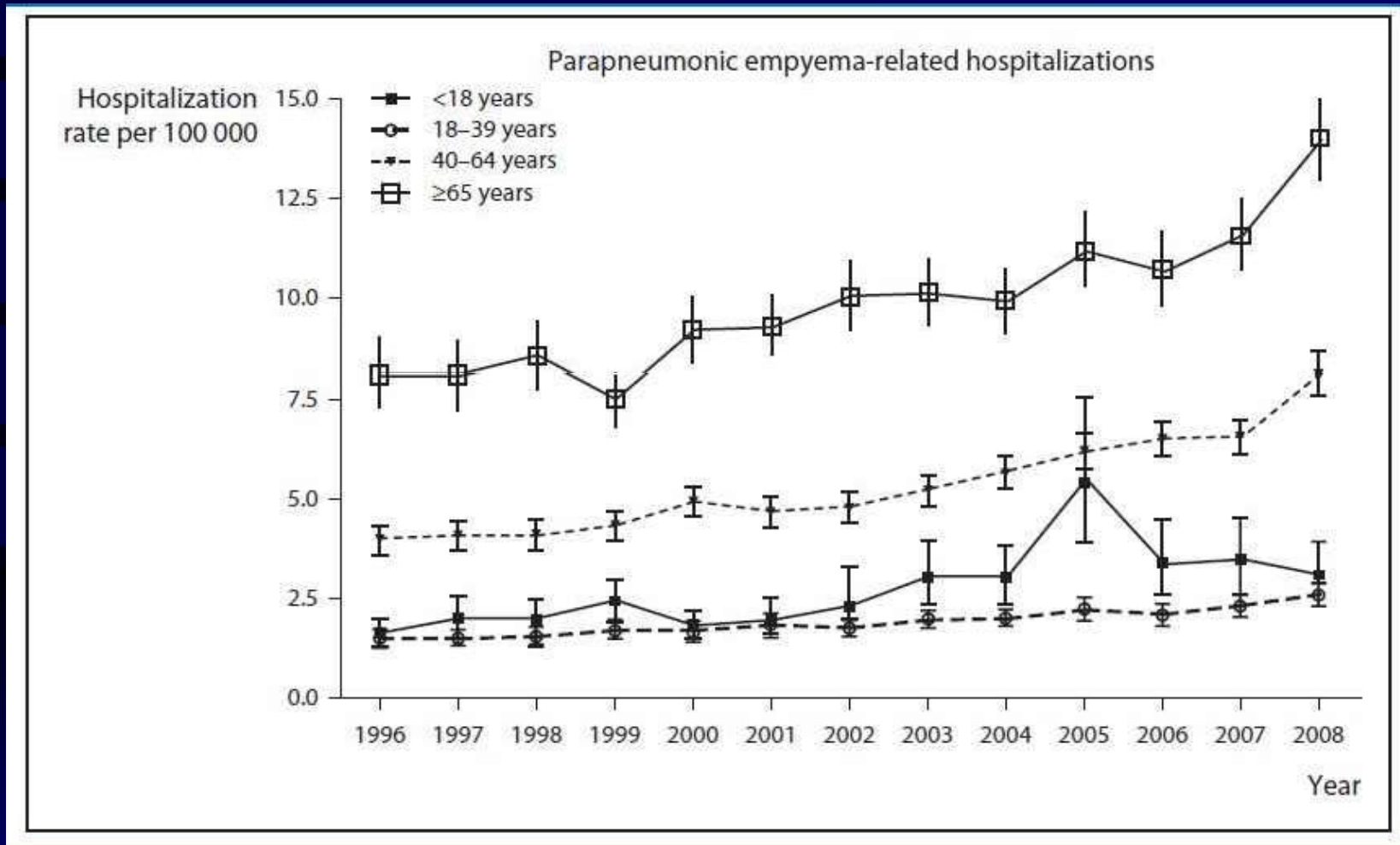
# **ROLE OF UROKINASE IN MANAGEMENT OF PARAPNEUMONIC EMPYEMA IN CHILDREN**

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# INTRODUCTION

- Empyema is defined as pus in the pleural space
- Complication of pneumonia, chest trauma, esophageal rupture, complication from lung surgery, or inoculation of the pleural cavity after thoracentesis or chest tube placement....

# Incidence of empyema increasing in US

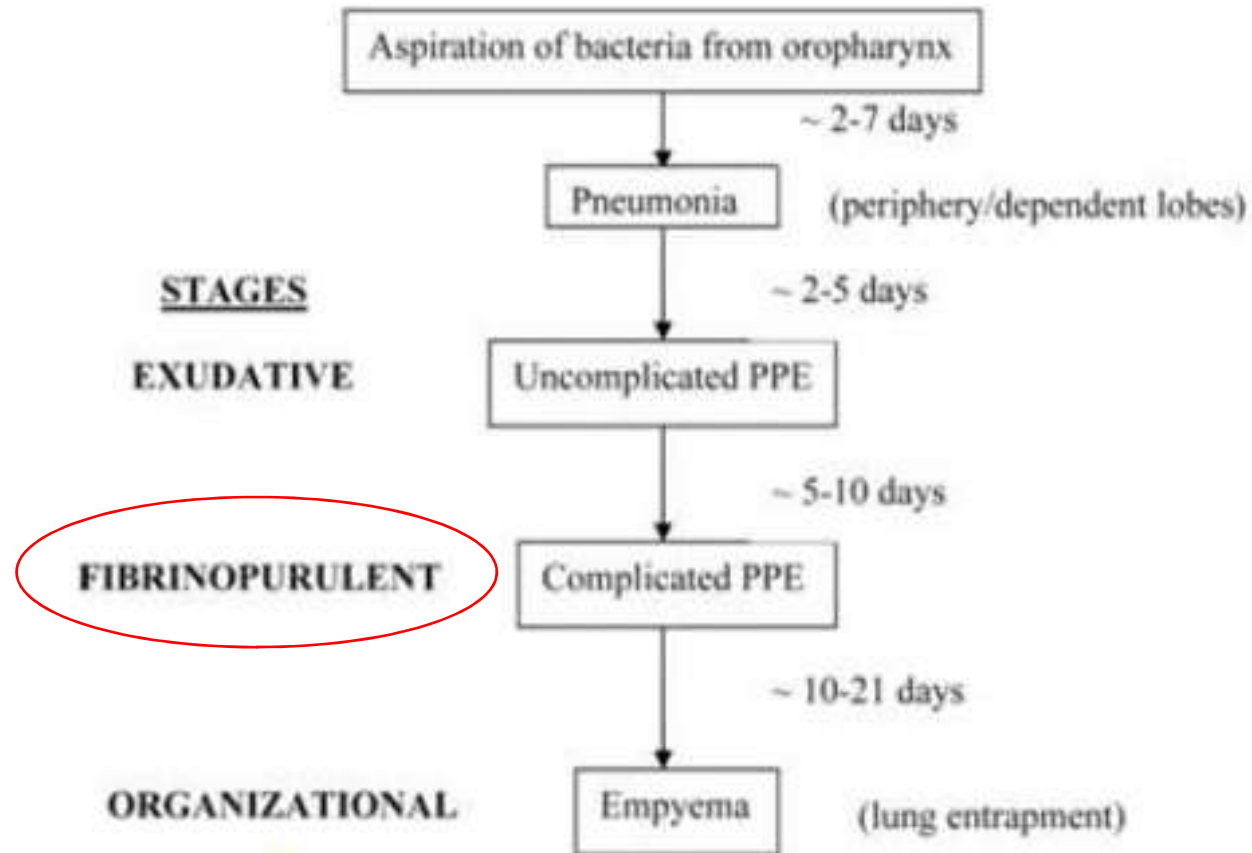


Trends in parapneumonic empyema-related hospitalization USA 1996-2008  
Data from Nationwide Inpatient Sample

## At Respiratory department 1- ND2

- 2015 : 55 cases
- 2016 : 35 cases

The estimated time course of untreated or inappropriately treated parapneumonic effusions.



Sahn S A Clin Infect Dis. 2007;45:1480-1486

## Step 2

- **VATS**
- **Fibrinolytic therapy**

# Video-assisted thoracoscopy (VATS)

- Primary modality for treating complicated empyema after initial therapy.
- Higher successful rate (90%) , shorter hospital stay
- Morbidity low, chest tube can be removed 3-4 day.

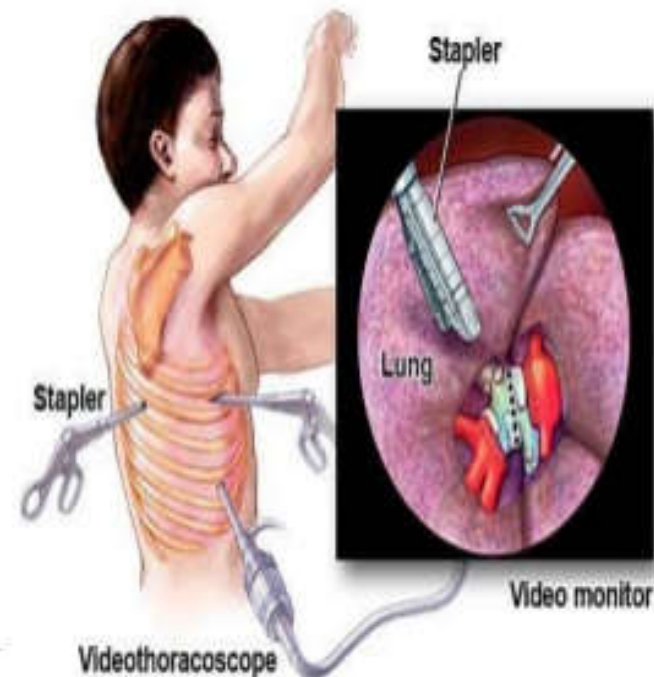
## Video assisted thoracoscopic surgery

VATS - achieves debridement of fibrinous pyogenic material, breakdown of loculations, and drainage of pus from the pleural cavity under direct vision. It leaves three small scars.

The use of early VATS (<48 hours after admission) versus late VATS (>48 hours after admission) significantly decreased the length of hospitalization

Karen D. Schultz, Leland L. Fan, Jay Pinsky, Lyssa Ochoa, E. O'Brian Smith, Sheldon L. Kaplan and Mary L. **The Changing Face of Pleural Empyemas in Children: Epidemiology and Management.**

Brandt *Pediatrics* 2004;113:1735





# Actually ???

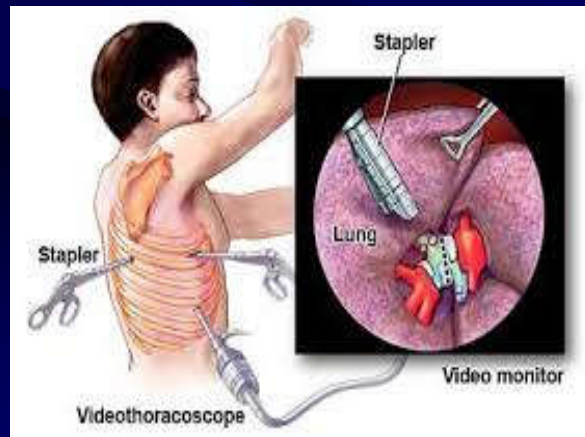


# VATS





# VATS



# Fibrinolytic Therapy Efficacy

# Cochrane 2004

## **Intra-pleural fibrinolytic therapy versus conservative management in the treatment of parapneumonic effusions and empyema (Review)**

Cameron R, Davies HR



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### **PLAIN LANGUAGE SUMMARY**

Too few participants in trials to recommend intrapleural therapy for complications following pneumonia

Sometimes in people with pneumonia who develop complications fibrinolytic therapy, which works by dissolving blood clots when they have fulfilled their role in preventing bleeding. We reviewed trials which studied the potential benefit and safety of adding intrapleural fibrinolytic therapy to intercostal tube drainage, which is normally used in these circumstances. We reviewed the effects of treatment in people over 14 years old. Fibrinolytics reduced length of hospital stay, time to defervescence (subsidence of fever), improvement in chest x-ray, treatment failure defined as death or requirement for surgery. Significant complications attributable to therapy were not seen. Although evidence suggests that intrapleural fibrinolysis can be considered as an important adjunctive therapy to intercostal tube drainage in these conditions, on the basis of RCT evidence alone, we cannot recommend the routine use of fibrinolysis in their management as the numbers are too small. In the studies streptokinase and urokinase work equally well, but streptokinase is slightly safer due to its lower complication rate.

# 2006

*Am J Respir Crit Care Med*, 2006 Jul 15;174(2):221-7. Epub 2006 May 4.

## Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema.

Sonnappa S, Cohen G, Owens CM, van Doorn C, Cairns J, Stanojevic S, Elliott MJ, Jaffé A.

### Author information

#### Abstract

**BACKGROUND:** Despite increasing incidence and morbidity, little evidence exists to inform the best management approach in childhood empyema.

**AIM:** To compare chest drain with intrapleural urokinase and primary video-assisted thoracoscopic surgery (VATS) for the treatment of childhood empyema.

**METHODS:** Children were prospectively randomized to receive either percutaneous chest drain with intrapleural urokinase or primary VATS. The primary outcome was the number of hospital days after intervention. Secondary end points were number of chest drain days, total hospital stay failure rate, radiologic outcome at 6 mo, and total treatment costs.

**RESULTS:** Sixty children were recruited. The two groups were well matched for demographics; baseline characteristics; and hematologic, biochemical, and bacteriologic parameters. No significant difference was found in length of hospital stay after intervention between the two groups: VATS (median [range], 6 [3-16] d) versus urokinase (6 [4-25] d) ( $p = 0.311$ ; 95% confidence interval, -2 to 1). No difference was demonstrated in total hospital stay: VATS versus urokinase (8 [4-17] d and 7 [4-25] d) ( $p = 0.645$ ); failure rate: 5 (16.6%); and radiologic outcome at 6 mo after intervention in both groups. The mean (median) treatment costs of patients in the urokinase arm US dollars 9,127 (US dollars 6,914) were significantly lower than those for the VATS arm US dollars 11,379 (US dollars 10,146) ( $p < 0.001$ ).

**CONCLUSIONS:** There is no difference in clinical outcome between intrapleural urokinase and VATS for the treatment of childhood empyema.

Urokinase is a more economic treatment option compared with VATS and should be the primary treatment of choice. This study provides an evidence base to guide the management of childhood empyema.

# 2014

## Urokinase versus VATS for treatment of empyema: a randomized multicenter clinical trial.

Marhuenda C<sup>1</sup>, Barceló C<sup>2</sup>, Fuentes I<sup>3</sup>, Guillén G<sup>2</sup>, Cano I<sup>4</sup>, López M<sup>4</sup>, Hernández F<sup>5</sup>, Pérez-Yarza EG<sup>6</sup>, Matute JA<sup>7</sup>, García-Casillas MA<sup>7</sup>, Alvarez V<sup>8</sup>, Moreno-Galdó A<sup>9</sup>.

### ⊕ Author information

#### Abstract

**BACKGROUND AND OBJECTIVE:** Parapneumonic empyema (PPE) is a frequent complication of acute bacterial pneumonia in children. There is limited evidence regarding the optimal treatment of this condition. The aim of this study was to compare the efficacy of drainage plus urokinase versus video-assisted thoracoscopic surgery in the treatment of PPE in childhood.

**METHODS:** This prospective, randomized, multicenter clinical trial enrolled patients aged <15 years and hospitalized with septated PPE. Study patients were randomized to receive urokinase or thoracoscopy. 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. The trial was approved by the ethics committees of all the participating hospitals.

**RESULTS:** A total of 103 patients were randomized to treatment and analyzed; 53 were treated with thoracoscopy and 50 with urokinase. There were no differences in demographic characteristics or in the main baseline characteristics between the 2 groups. 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 = .47).

**CONCLUSIONS:** Drainage plus urokinase instillation is as effective as video-assisted thoracoscopic surgery as first-line treatment of septated PPE in children.

# 2014

*Clin Respir J*. 2014 Jul;8(3):281-91. doi: 10.1111/crj.12068. Epub 2014 Jan 16.

## **Efficacy of intrapleural instillation of fibrinolytics for treating pleural empyema and parapneumonic effusion: a meta-analysis of randomized control trials.**

Nie W<sup>1</sup>, Liu Y, Ye J, Shi L, Shao F, Ying K, Zhang R.

### ⊕ Author information

#### Abstract

**INTRODUCTION:** The effects of intrapleural fibrinolysis for treating pleural empyema and parapneumonic effusion remain uncertain.

**OBJECTIVES:** We conducted a meta-analysis of published randomized controlled trials (RCTs) to evaluate the efficacy of intrapleural instillation of fibrinolytics for treating pleural empyema and parapneumonic effusion.

**METHODS:** Medline, Web of Science, Ovid and regulatory documents up to June 10, 2012 were searched. We selected RCTs on intrapleural fibrinolysis vs placebo control treatment for pleural empyema and parapneumonic effusion. The meta-analysis was used to determine the odds ratios (OR) for death, surgical intervention and severe side effects, and weighted mean differences were used to estimate lengths of hospital stays.

**RESULTS:** Ten trials with a total of 977 patients were included. Compared with a placebo, intrapleural fibrinolytic therapy **decreased the OR for surgical intervention [OR = 0.24; 95% confidence interval (CI): 0.10-0.60] and the length of hospital stays (weighted mean difference = -6.47; 95% CI: -8.87, -4.08).** Intrapleural fibrinolysis was associated with a non-significant reduction in mortality rate (OR = 1.16; 95% CI: 0.71-1.89) and a non-significant increase in severe side effects (OR = 1.92; 95% CI: 0.87-4.21). Subgroup analyses indicated that urokinase agents had marked positive effects on reducing surgical intervention (OR = 0.33; 95% CI: 0.14-0.78), but neither streptokinase nor tissue plasminogen activator did.

**CONCLUSIONS:** The present results show that intrapleural fibrinolysis with urokinase may be potentially effective for reducing the need for surgery. Intrapleural fibrinolytic therapy is effective for shortening the lengths of hospital stays without increasing the incidence of severe side effects.

*Clin Respir J* 2014 Jul; 8(3):281-9, doi: 10.111/crj.12068. Epub 2014 Jan14



# 2015

**Initial treatment of septated parapneumonic empyema with drainage plus fibrinolytic agents is equally effective as video-assisted thoracoscopic surgery, and is suitable as first-line therapy.**

Shirota C<sup>1</sup>, Uchida H<sup>1</sup>.

⊕ Author information

## Abstract

It is thought that 0.6-2% of cases of pneumonia in children are complicated by parapneumonic empyema. The mainstay treatment options for empyema are pleural chest drainage plus fibrinolysis or video-assisted thoracoscopic surgery (VATS). Marhuenda et al. reported the results of a prospective, multicenter, clinical trial in which patients with parapneumonic empyema were randomized to either drainage plus urokinase or to VATS. That showed that the median postoperative stay, median hospital stay, and number of febrile days after treatment were not significantly different between the VATS group and the urokinase group. Only three other prospective randomized trials have been conducted with the same objective. The results in these studies had partially different among four trials. But all studies described that it is apparent that VATS is not more effective than fibrinolytic treatment. Intrapleural fibrinolytic treatment, which is much less invasive and lower inexpensive than VATS, is an effective and safe alternative to surgical treatment of complicated empyema. VATS would be reserved for patients who fail to respond to chemical/enzymatic debridement. We need additional randomized controlled trials with relevant inclusion/exclusion criteria and adequate sample sizes to determine the optimal therapy for parapneumonic-complicated empyema in children.

Translation Pediatric, 2015

# Uptodate 2016

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## Summary of the data from a systematic review of primary operative versus nonoperative therapy for pediatric empyema

поменя  
прокс



| Outcome                                | Antibiotics and chest tube (N = 3183) | Fibrinolytic therapy* (N = 64)    | VATS <sup>†</sup> (N = 176) | Thoracotomy (N = 17) |
|--|---------------------------------------|-----------------------------------|-----------------------------|----------------------|
| Mortality rate (range)                 | 3.3 percent (0 to 35 percent)         | 0 percent                         | 0 percent                   | 0 percent            |
| Failure rate <sup>Δ</sup> (range)      | 23.6 percent (0 to 67 percent)        | 9.4 percent (6.7 to 14.2 percent) | 2.8 percent                 | 3.1 percent          |
| Length of stay                         | 20 ± 8.3 days                         | 10.7 ± 5.1 days                   | 11.2 days                   | 10.6 days            |
| Duration of chest tube                 | 10.6 ± 3.4 days                       | 4 days                            | 4 days                      | 6.2 days             |
| Duration of antibiotics                | 21.3 ± 7.9 days                       | Not specified                     | 13.2 days                   | Not specified        |
| Complication rate <sup>◇</sup> (range) | 5.6 percent (0 to 45 percent)         | 12.5 percent (0 to 16.6 percent)  | 5.4 percent                 | 5.2 percent          |

- A randomized trial in Europe compared VATS to medical therapy with fibrinolysis and found no difference in clinical outcome [34]. In this trial, 60 children (<16 years) with radiographic evidence of empyema and indications for drainage were randomly assigned to treatment with primary VATS or percutaneous chest tube drainage with intrapleural urokinase. The primary outcome measure was length of hospital stay after intervention and there was no difference between groups (95% CI -2 to 1 day). The median hospital stay after intervention was 6 days for both groups, with a range of 3 to 16 days for those treated with VATS and 4 to 25 days for those randomized to fibrinolysis. Hospital costs were 25 percent higher for the group treated with primary VATS versus those randomized to primary fibrinolysis. Of note, the fibrinolytic used in this trial was urokinase, which is less expensive than the fibrinolytic agents commonly used in the United States.
- Similar findings were shown in a randomized trial from the United States, in which 36 children were randomized to initial treatment with primary VATS or fibrinolysis with alteplase (recombinant human tissue plasminogen activator [tPA]) [35]. The failure rate of fibrinolysis was 16.6 percent (3 of 18 subjects), and two patients treated with primary VATS required ventilator support after surgery. There was no difference in median hospital stay after intervention, but hospital costs were substantially lower for the group treated with primary fibrinolysis (USD \$11,700 versus \$7,600).

# 2016

J Pediatr Surg. 2016 Apr;51(4):588-91. doi: 10.1016/j.jpedsurg.2015.07.022. Epub 2015 Aug 12.

## 'Less may be best'-Pediatric parapneumonic effusion and empyema management: Lessons from a UK center.

Long AM<sup>1</sup>, Smith-Williams J<sup>2</sup>, Mayell S<sup>3</sup>, Couriel J<sup>3</sup>, Jones MO<sup>1</sup>, Losty PD<sup>4</sup>.

### ⊕ Author information

#### Abstract

**BACKGROUND:** Children with empyema are managed at our center using a protocol-driven clinical care pathway. Chemical fibrinolysis is deployed as first-line management for significant pleural disease. We therefore examined clinical outcome(s) to benchmark standards of care while analyzing disease severity with introduction of the pneumococcal conjugate vaccine.

**METHODS:** Medical case-records of children managed at a UK pediatric center were surveyed from Jan 2006 to Dec 2012. Binary logistic regression was utilized to study failure of fibrinolytic therapy. The effects of age, comorbidity, number of days of intravenous antibiotics prior to drainage and whether initial imaging showed evidence of necrotizing disease were also studied.

**RESULTS:** A total of 239 children were treated [age range 4months-19years; median 4years]. A decreasing number of patients presenting year-on-year since 2006 with complicated pleural infections was observed. The majority of children were successfully managed without surgery using antibiotics alone (27%) or a fine-bore chest-drain and urokinase (71%). Only 2% of cases required primary thoracotomy. 14.7% cases failed fibrinolysis and required a second intervention. The only factor predictive of failure and need for surgery was suspicion of necrotizing disease on initial imaging (P=0.002, OR 8.69).

**CONCLUSION:** Pediatric patients with pleural empyema have good outcomes when clinical care is led by a multidisciplinary team and protocol driven care pathway. Using a 'less is best' approach few children require surgery.

# CHOICE OF AGENT

- Streptokinase and Streptodornase : Significant systemic reaction, unsatisfactory, pleural bleeding
- Purified streptokinase, urokinase ;Not allergic
- Success rate: 80% for streptokinase ( 250000 U/100ml normal saline ) , 90% for urokinase ( 100000U/100ml normal saline ) .
- Only urokinase has been studied in a placebo-controlled fashion in children, and thus is recommended by the BTS

# CONCLUSION

Loculated fluid or empyema — Patients who have loculated pleural fluid documented by ultrasonography can be treated with either antibiotics alone, pleural catheter placement with fibrinolytics, or surgical therapy (VATS) ([algorithm 2](#)).

- We suggest pleural drainage via small-bore chest tube (pigtail catheter) with fibrinolysis and antibiotics as the initial treatment of choice for children with loculated effusions ([Grade 2C](#)). However early VATS is an acceptable alternative, and may be the first-line option in centers with surgeons experienced with VATS. The choice may be influenced by available expertise, cost considerations, and patient preferences. Pleural drainage with fibrinolysis is successful in approximately 80 percent of children; the remainder who fail medical therapy will require VATS. (See ['Intrapleural fibrinolytics versus surgical treatment'](#) above and ['Fibrinolytic therapy'](#) above.)

Uptodate 5.2016

# CONCLUSION

- Intrapleural fibrinolytics shorten hospital stay and are recommended for any complicated parapneumoic effusion (thick fluid with loculations) or empyema (overt pus): **[B]** (**BTS Guidelines 2014**)
- There is no evidence that any of the three fibrinolytics are more effective than others, but only urokinase has been studied in RCTs in children is recommended : **[B]** (**BTS Guidelines 2014**)
- Tube thoracostomy with the subsequent instillation of fibrinolytic agents should be attempted as the initial treatment for pediatric patients with an empyema **[1A]** (**AATS Guidelines 2014**)

# Trends in Treatment of Infectious Parapneumonic Effusions in U.S

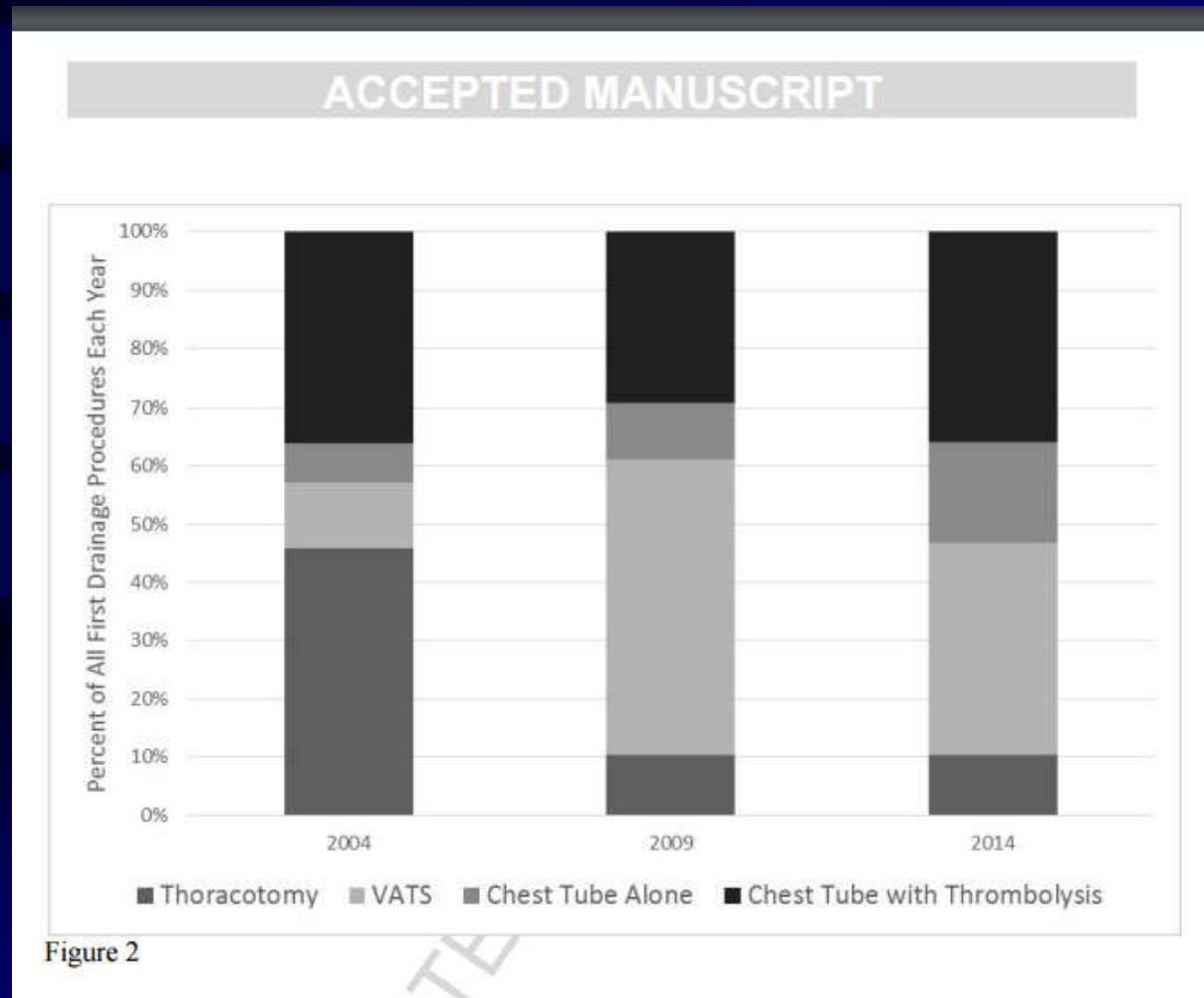


Figure 2

**THANK YOU FOR  
YOUR ATTENTION!!!!**