Outcomes & Clinical Trials Update: Empyema & NEC

American Pediatric Surgical Association
Outcomes & Clinical Trials Committee

Fizan Abdullah, Chair
Saleem Islam, Vice Chair
Gudrun Aspelund
Catherine C. Chen
Shawn J. Rangel
Eunice Huang
Cynthia D. Downard
Adam Goldin
Shawn St. Peter
Casey M. Calkins
Douglas C. Barnhart
Jackie M. Saito
Martin L. Blakely
Laura Cassidy, Ex Officio
Marjorie J. Arca, Ex Officio
Outcomes & Clinical Trials Update: Empyema & NEC

American Pediatric Surgical Association
Outcomes & Clinical Trials Committee

Introduction

Empyema Review Summary 20 mins
Questions to Panel 10 mins

NEC Review Summary 20 mins
Questions to Panel 10 mins
### Classes of Evidence

*Oxford Centre for Evidence-based Medicine Levels of Evidence, March 2009. [www.cebm.net](http://www.cebm.net)*

<table>
<thead>
<tr>
<th>Grades of Recommendation</th>
<th>Classes of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Consistent Level I Studies</td>
</tr>
<tr>
<td>B</td>
<td>Consistent Level II or III studies or extrapolation from Level I studies</td>
</tr>
<tr>
<td>C</td>
<td>Level IV studies or extrapolations from Level II or III studies</td>
</tr>
<tr>
<td>D</td>
<td>Level V evidence or inconsistent or inconclusive studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Systematic review of RCT’s or RCT with narrow CI</td>
</tr>
<tr>
<td>II</td>
<td>Cohort studies, low quality RCT’s, outcomes research</td>
</tr>
<tr>
<td>III</td>
<td>Case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Case series</td>
</tr>
<tr>
<td>V</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
American Pediatric Surgical Association
Outcomes & Clinical Trials Committee

Major Scope of Activities 2011-2012

I. Systematic Reviews

II. Review of Literature to generate E-Blasts

III. Survey Screening & Implementation
American Pediatric Surgical Association
Outcomes & Clinical Trials Committee

Major Scope of Activities 2011-2012

I. Systematic Reviews

Outcomes Research
Survey Methodology
Antibiotics for Appendicitis
Abdominal Wall Defects
Strategies for Prevention of Central Line Infection
Parenteral-Nutrition Associated Cholestasis
Empyema: Questions

- Does the distinction between “parapneumonic effusion” and “empyema” affect clinical decision-making?
- What is the optimal imaging modality in evaluating pleural space disease?
- When and how should pleural fluid be managed?
- What is the best treatment option and optimal timing for the management of empyema?
- What is the optimal chemical debridement agent for empyema?
- What therapeutic options exist if chemical debridement fails?
- What is the best therapeutic modality for parenchymal abscess or necrotizing pneumonia?
- What should be the duration of antibiotic therapy after an intervention?
Review: Empyema in Children

Saleem Islam & Shawn D St Peter
On Behalf of APSA Outcomes & Clinical Trials Committee
Disclosures

- Nothing to disclose
Parapneumonic Effusion vs. Empyema: Does anyone care?

- Various staging schema proposed
- Radiologic, chemical and clinical criteria used
- Pre collection stage
  - Exudative phase – pH>7.2
  - Fibrinopurulent stage – pH<7.2
- Organizing phase -
<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Small Nonsignificant Parapneumonic effusion</td>
<td>&lt;10 mm thick on decubitus x-ray No thoracentesis indicated</td>
</tr>
<tr>
<td>2</td>
<td>&gt;10 mm thick Typical Parapneumonic effusion</td>
<td>Glucose &gt;40 mg/dL, pH&gt;7.20 Gram stain and culture negative Antibiotics alone</td>
</tr>
<tr>
<td>3</td>
<td>7.00&lt;pH&lt;7.20 and/or LDH&gt;1,000 and glucose&gt;40 mg/dL Borderline complicated Parapneumonic effusion</td>
<td>Gram stain and culture negative Antibiotics plus serial thoracentesis</td>
</tr>
<tr>
<td>4</td>
<td>pH&lt;7.00 and/or glucose &lt;40 mg/dL and/or Simple complicated Parapneumonic effusion</td>
<td>Gram stain or culture positive Not loculated not frank pus Tube thoracostomy plus antibiotics</td>
</tr>
<tr>
<td>5</td>
<td>pH&lt;7.00 and/or glucose &lt;40 mg/dL and/or Complex complicated Parapneumonic effusion</td>
<td>Gram stain or culture positive Multiloculated Tube thoracostomy plus thrombolytics (Rarely require thoracoscopy or decortication)</td>
</tr>
<tr>
<td>6</td>
<td>Frank pus present Simple empyema</td>
<td>Single locule or free flowing Tube thoracostomy±decortication</td>
</tr>
<tr>
<td>7</td>
<td>Frank pus present Complex empyema</td>
<td>Multiple locules Tube thoracostomy+thrombolytics Often require thoracoscopy or decortication</td>
</tr>
</tbody>
</table>
Stage I
(No loculations on imaging studies)

1) Drainage (Thoracentesis or chest tube)
2) Antibiotics

Stage II
(Loculations on imaging studies)

1) Fibrinolytic therapy (Thoracoscopy for failures)
2) Antibiotics

Stage III
(Organizing stage, fibrous peel)

1) Likely need thoracotomy (Thoracoscopy may be possible in selected patients)
2) Antibiotics
Parapneumonic Effusion vs Empyema

- Adult data suggest that the use of these staging schemes may help in management
- Level of evidence is poor
- **Recommendation:** Most children have management based on imaging alone (Class D Evidence)
What Imaging to Perform?

- CXR: PA and lateral - 2 D view – adult data with high rate of missing effusions
- CT Scan: High Radiation dose
- Ultrasound: Availability and interpretation
- MRI: Not done
Imaging Continued

• Accuracy of US and CT fairly equivalent
• US superior in detection of pleural stranding and fibrin. Prospective data showed no benefit to CT
• Ability to distinguish free flowing from thick equal –may be better for loculations
• Able to detect parenchymal collections well
• Data from two hospitals implementing clinical pathways showed decrease in CT use with no change in outcomes
Imaging Recommendation

- **Recommend** US whenever possible, however CT is appropriate if needed for preop planning.
- Recognize that US is not always available at all institutions, and certain body habitus may prevent its use.
- Level C evidence
TRADITION

JUST BECAUSE YOU’VE ALWAYS DONE IT THAT WAY DOESN’T MEAN IT’S NOT INCREDIBLY STUPID.
When Should Pleural Fluid Be managed

- **Size:** based on standard CXR – adult data
  - 10 mm rim, 1-2 cm, or greater than 2 cm (Decube)
  - <1/4<sup>th</sup> chest, 1/4<sup>th</sup>-1/2, and greater than ½ on upright

- Retrospective study in children – small and moderate effusions do not need drainage, and the large ones are symptomatic.

- **Symptoms:** respiratory distress, issues related to mediastinal shift
When Should Pleural Fluid Be managed?

- **Loculations:** Imaging (US or CT) reveals a complex collection with multiple loculated components. Moderate correlation with purulent material.

- **Recommendation:** intervention indicated in large and symptomatic effusions, or loculated one (Level C Evidence)
How should Pleural Fluid be managed?

- Expectant management
- Single thoracentesis – for a simple effusion, appropriate patient.
- Multiple procedures can be performed and are effective. Prospective study from Israel compared QOD aspirations vs chest tube with no difference in LOS.
- Would recommend placing tube if need to go more than once
How should Pleural Fluid be managed?

- Tube thoracostomy – better to place a tube rather than multiple separate procedures (BTS recommendations – Level D)
- Smaller size is better – equal efficacy, less pain – adult study comparing less than 14 Fr vs. larger
- Retrospective pediatric study compared standard CT with pigtail and found no differences

**Recommend** small size tube if needed

(Lever C Evidence)

VATS and Fibrinolysis
BLAME

THE SECRET to SUCCESS is KNOWING WHO to BLAME for YOUR FAILURES.
What is the optimal timing and first treatment option for management of empyema?
Primary Option and Timing of Definitive Management

- The definitive management has been shown to be debridement of the pleural space by either chemical or mechanical means
- Chemical debridement – fibrinolysis
- Mechanical debridement - VATS
Primary Option and Timing of Definitive Management

FIBRINOLYSIS

- When the pleural space becomes infected, the ensuing inflammatory reaction is associated with fibrin deposition and decreased fibrinolytic activity.

- The procoagulant environment leads to the development of solid material in the form of septations or loculations.

- Fibrin is a predominant component of the extracellular matrix.

- Instillation of a fibrinolytic agent may liquefy pleural space disease.
Primary Option and Timing of Definitive Management

**FIBRINOLYSIS**

- Has been shown to be superior to chest tube drainage alone in retrospective and prospective studies

**VATS**

- Has been shown to be superior to chest tube drainage alone in retrospective and prospective studies
Comparing Primary VATS to Primary Fibrinolysis

Two Prospective, Randomized Trials

- One was conducted in London, one in the U.S.
- Primary outcome was LOS in both trials
- Both initiated therapy in both arms upon diagnosis of empyema
- Both utilized 3 instillations of fibrinolytics each 24 hours apart
London Prospective Trial

- 60 patients
- Urokinase was fibrinolytic
- 4 hour dwell time

U.S. Prospective Trial

- 36 patients
- tPA was fibrinolytic
- 1 hour dwell time
## Prospective Trials

### VATS v Fibrinolysis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm</td>
<td>VATS</td>
<td>P Value</td>
<td>tPA</td>
</tr>
<tr>
<td>Length of Stay (Days)</td>
<td>Urokinase</td>
<td>6</td>
<td>6</td>
<td>0.33</td>
</tr>
<tr>
<td>Charges*</td>
<td>9.1K</td>
<td>11.3K</td>
<td>&lt;0.001</td>
<td>7.5K</td>
</tr>
<tr>
<td>Failure Rate</td>
<td>16.6%</td>
<td></td>
<td></td>
<td>16.6%</td>
</tr>
</tbody>
</table>
## U.S. STUDY RESULTS

### Outcomes

<table>
<thead>
<tr>
<th></th>
<th>VATS</th>
<th>tPA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (Days)</td>
<td>6.89</td>
<td>6.83</td>
<td>0.96</td>
</tr>
<tr>
<td>O2 tx (Days)</td>
<td>2.25</td>
<td>2.33</td>
<td>0.89</td>
</tr>
<tr>
<td>PO Fever (Days)</td>
<td>3.1</td>
<td>3.8</td>
<td>0.46</td>
</tr>
<tr>
<td>Analgesic doses</td>
<td>22.3</td>
<td>21.4</td>
<td>0.90</td>
</tr>
</tbody>
</table>
VATS v Fibrinolysis

Summary

- No recovery advantages to VATS
- Fibrinolysis is less costly
- Avoids an operation in the majority
VATS v Fibrinolysis

Caveats

- Tubes were able to be placed at the bedside in both trials
- VATS was not inferior and remains the other option if fibrinolysis is not feasible
Algorithm

EMPYEMA
(Loculations or > 10,000 WBC/µL)

↓

12 Fr chest tube with 3 doses of tPA

↓

Drainage decreased without clinical improvement

↓

Ultrasound or CT

Persistent pleural space disease

No pleural space disease

↓

VATS

Continue Antibiotics
Timing of Definitive Management

- Fibrinolysis and VATS have been shown to be superior to chest tube alone but equal when initiated upon diagnosis.
- Both trials did not initially treat empyema with chest tube alone.
- Regardless of using chemical or mechanical debridement, it should be instituted upon diagnosis of empyema.
What is the optimal timing and first treatment option for management of empyema?

**Grade B recommendation:** Once an effusion is diagnosed as empyema, definitive management should be initiated with mechanical or chemical debridement.

**Grade A recommendation:** Operative management should be reserved for patients who fail to respond to chemical debridement if healthcare resources allow for such management.
What is the best agent for chemical debridement?
Fibrinolytic v Saline

- One trial in 60 children comparing urokinase to saline found 2 day reduction in length of stay with urokinase
## Fibrinolytic v Saline

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Agent</th>
<th>Failure Fibrinolysis</th>
<th>Failure Saline</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies 1999</td>
<td>24</td>
<td>Streptokinase</td>
<td>0%</td>
<td>25%</td>
<td>0.14 (0.01-2.50)</td>
</tr>
<tr>
<td>Bouros 1999</td>
<td>31</td>
<td>Urokinase</td>
<td>13.3%</td>
<td>37.5%</td>
<td>0.36 (0.08-1.50)</td>
</tr>
<tr>
<td>Tuncozgur 2001</td>
<td>49</td>
<td>Urokinase</td>
<td>29.2%</td>
<td>60.0%</td>
<td>0.49 (0.24-0.98)</td>
</tr>
<tr>
<td>Diacon 2004</td>
<td>44</td>
<td>Streptokinase</td>
<td>13.6%</td>
<td>45.5%</td>
<td>0.30 (0.10-0.94)</td>
</tr>
<tr>
<td>Maskell 2005</td>
<td>454</td>
<td>Streptokinase</td>
<td>15.5%</td>
<td>14.8%</td>
<td>1.07 (0.68-1.69)</td>
</tr>
</tbody>
</table>

Treatment failure is defined as need for an operation for mechanical debridement. Composite risk ratio from 2 meta-analyses were 0.53 (0.28-1.02) and 0.71 (0.50-0.99).
Optimal Agent for Chemical Debridement

- One trial in 50 adults comparing urokinase to streptokinase found no difference in outcomes
- Direct comparative data between tPA and other fibrinolytic agents does not exist
  - tPA and urokinase performed the same in the 2 trials
- Urokinase and streptokinase not available in U.S.
- Addition of DNase?
Prospective, Randomized Trial

- Adult patients – 50 patients in 4 arms
  - tPA/DNase, tPA only, DNase only, saline only
  - tPA/DNase showed better clearance on CXR
  - tPA/DNase had lower LOS compared to saline and similar to tPA alone
  - tPA/DNase and tPA had lowest failure rate (4 and 6%)
What is the best agent for chemical debridement?

Grade B recommendation: The current data suggest fibrinolytics benefit those with solid material in the pleural space. DNase may be advantageous when added to fibrinolytics in adults.
What therapeutic options exist if chemical debridement fails?
Deciding if Chemical Debridement Fails

- Fever over 38 after 4 days
  - Definition in London trial
- We currently define persistent illness requiring VATS as oxygen requirements or poor PO intake with untreated pleural space disease accounting for it
What therapeutic options exist if chemical debridement fails?

Grade D recommendation: Consideration for VATS after chemical debridement should occur when the patient is persistently ill after the chest tube drainage is diminished and imaging proves substantial pleural space disease.
Treatment of Necrotizing Pneumonia or Abscess

- Can usually be treated with antibiotics alone
- Well localized and peripheral abscesses have been reported to be drained
- Generally avoid an operation due to risks

Grade D recommendation: Parenchymal abscess and necrosis should be managed non-operatively. If VATS is necessary due to concomitant pleural space disease, caution should be taken with lung manipulation.
Duration of Antibiotic Therapy after an Intervention

- The standing recommendation is to continue therapy for 2 - 4 weeks.
- Recent consensus guidelines suggest to continue treatment for approximately 10-days after resolution of fever.

Grade D recommendation.
1) Does the distinction between “parapneumonic effusion” and “empyema” affect clinical decision-making?

There are no data that correlate stages of effusion with management strategies.

2) What is the optimal imaging modality in evaluating pleural space disease?

Grade C recommendation: Ultrasound should be the initial and primary modality to evaluate empyema. CT should be reserved for more complicated disease.

3) When and how should pleural fluid be managed?

Grade C recommendation: Fluid evacuation should be considered in large, loculated, and/or associated with symptoms. Methods may include one time or multiple thoracentesis or placement of a small tube, depending on the clinical situation. Thoracotomy should not be routinely included in the primary management of empyema.
4) What is the optimal timing and first treatment option for management of empyema?

- **Grade B recommendation**: Once an effusion is diagnosed as empyema, definitive management should be initiated with mechanical or chemical debridement. Chemical and mechanical debridements have been shown to have equivalent outcomes in two prospective trials. Since chemical debridement does not require an operation, it is reasonable to utilize chemical debridement as first line therapy.

- **Grade A recommendation**: Operative management should be reserved for patients who fail to respond to chemical debridement if healthcare resources allow for such management.

5) What is the best agent for chemical debridement?

- **Grade B recommendation**: A fibrinolytic agent in the irrigation fluid during thoracostomy debridement is advantageous in children according to a single prospective trial. The current data suggest fibrinolytic benefit with solid material in the pleural space. DNase may be advantageous when added to fibrinolytics in adults.
6) What therapeutic options exist if chemical debridement fails?
   • **Grade D recommendation:** Consideration for VATS after chemical debridement should occur when the patient is persistently ill after the chest tube drainage is diminished and imaging proves substantial pleural space disease.

7) What is the best therapeutic modality for parenchymal abscess or necrotizing pneumonia?
   • **Grade D recommendation:** Parenchymal abscess and necrosis should be managed non-operatively. If fibrinolysis/VATS is necessary due to concomitant pleural space disease, caution should be taken with lung manipulation.

8) What should the duration of antibiotic therapy be after an intervention?
   • **Grade D recommendation:** Therapy should continue for a minimum of ten days after the resolution of fever.