Cook Children's Medical Center
Clinical Excellence Committee

Evidence based pathway for the diagnosis and management of empyema

Goals:

-To deliver high quality, evidence-based care using the latest literature and national guidelines
-To decrease variation in care between providers
-To reduce unnecessary interventions that may cause harm, increase cost or increase length of stay.

Inclusion Criteria:

-Children and adolescents with empyema

Exclusion Criteria:

-Concern for non-infectious etiology
-Patients with immunodeficiency

Background:

Despite the widespread availability of the pneumococcal conjugate vaccine and decreasing rates of pneumonia, the incidence of empyema in children is increasing. Empyema is the most frequent suppurative complication of bacterial pneumonia in children and it has been estimated that 0.6-2% of pediatric pneumonia cases are complicated by empyema [1, 2].

Parapneumonic effusions exist on a continuum of disease with empyema that is thought to occur in 3-4 stages of increasing complexity [2].

Stage 1 (Pre-Collection Stage): This stage does not involve a fluid collection and occurs when there is a pneumonia with pleuritis and inflammation.
Stage 2 (Exudative Stage): This stage involves a simple parapneumonic effusion that is clear, free-flowing and contains a lower white count. This stage may or may not advance to more complicated stages.
Stage 3 (Fibrinopurulent Stage): This stage involves a complicated parapneumonic effusion with deposition of fibrin and purulent material in the pleural space. Fibrin strands and septations begin to appear and the white cell count of the fluid begins to increase.
Stage 4 (Organizational Stage): A thick pleural peel is formed, which can cause chronic restrictive lung disease. This stage rarely occurs in children.

While the above progression of parapneumonic effusion and empyema is helpful in understanding the pathophysiology, it does not necessarily affect treatment [2]. Historically, empyemas were treated with antibiotics and chest tube drainage, however these treatments were associated with prolonged length of stay and high failure rates [3]. In addition to thoracotomy, two less invasive empyema treatments have been used that include chest tube placement with instillation of fibrinolytic agents and video-assisted thoracoscopic surgery (VATS). Both of these techniques have been shown to allow for a

faster recovery time. Studies that have examined the difference between VATS and fibrinolytic therapy for first-line management of empyema have shown the two to be equivalent, though fibrinolytic therapy was found to result in significantly less cost [4].

The following recommendations are consistent with national guidelines and standards of care for the diagnosis and management of empyema in children.

1. **Diagnosis**
    a. **Chest ultrasound should be the primary imaging modality to evaluate concerns for possible pleural space disease on chest x-ray. US can accurately identify loculations and solid components of the disease process. Chest CT should be reserved for more complicated cases where further information may direct surgical decision-making or if US would not provide adequate imaging, for example due to a patient's body habitus [2].**

        Based on chest x-ray, it can be difficult to distinguish pleural fluid from parenchymal consolidation [5]. US can accurately identify the presence of loculations, differentiate pleural fluid from consolidation, estimate the size of the effusion and guide chest tube placement. It is portable, less invasive, does not involve ionizing radiation and is cheaper than CT [6]. With increasing awareness of the possible long-term cancer risks that come with cumulative CT exposure, there is greater concern regarding routine CT use [7]. CT has also been shown to be less effective than US at identifying septations or fibrin strands within a pleural fluid collection [8]. CT should only be used for more complex cases, when it would affect medical decision making, or in situations where US does not provide adequate imaging.

        It is important to note that one difference between adult and pediatric empyema management is the role of chest CT. The 2017 adult empyema guidelines do recommend a chest CT be obtained if pleural space infection is suspected [9], while pediatric recommendations are that CT not be routinely used. The reason for this difference is that a significant percentage of adult empyema cases are the result of underlying abnormalities, other than pneumonia. In pediatrics, the vast of majority of children with empyema have a normal underlying lung and their empyema is the result of an underlying bacterial pneumonia [10].

    b. **Repeat chest x-ray should be obtained in patients with pneumonia who fail to show adequate improvement after 48-72 hours from initiation of antibiotics. It should also be obtained in patients with pneumonia who demonstrate clinical deterioration [11].**

2. **Indications for drainage of pleural fluid**
    a. **Size**

        On upright chest x-rays, a small effusion will result in opacification of less than ¼ of the hemithorax. A moderate effusion will result in opacification of ¼ - ½ of the hemithorax. A large effusion will result in opacification of more than ½ of the hemithorax. A retrospective study found that a significant amount of children with small or medium effusions could be treated with antibiotics alone, while the presence of a large effusion was a strong indicator for the need for drainage. This same study found that larger pleural effusions in children were more often symptomatic, which led to drainage based on symptoms and not size alone [12]. The literature and national guidelines offer contradicting guidance for moderate effusions that are loculated with no significant respiratory distress [2, 11-13]. Provider discretion is advised, based on the patient's clinical characteristics and family/patient preferences. The provider should weigh the likelihood of success with non-surgical interventions with the importance of early surgical intervention, if needed.

        Ultrasound may also be used to estimate pleural effusion size.

        While chest x-ray is a useful tool to estimate the size of an effusion, chest x-ray alone should not be used for surgical decision-making. The imaging modality that should be used for surgical decision making, the majority of the time, remains chest ultrasound [2].

    b. **Symptoms**

        Worsening symptoms, such as fever, tachypnea or increasing oxygen requirement, may result in the need for drainage of pleural fluid. Poor response to medical therapy may also result in a need for drainage of pleural fluid. Several studies have found that respiratory distress on admission correlated with the need for intervention and prolonged length of stay [12, 14].

    c. **Loculations**

        While at least one study showed an association with the presence of loculations and the need for drainage [14], another study did not find an association between the two [12].

3. **Draining of pleural fluid**
    a. **Chest tube placement with instillation of fibrinolytics should be considered first line therapy for drainage of parapneumonic fluid collections over VATS [2].**

        Current national guidelines recommend chest tube placement with fibrinolytic therapy as first-line treatment for the management of empyema over VATS because both have equivalent outcomes, but

chest tube placement with fibrinolytic therapy is less invasive, may not require general anesthesia and is more cost-effective.

Multiple studies have been done that show equivalent outcomes when comparing chest tube placement with fibrinolytic therapy compared to VATS [1, 4, 15]. These studies found no difference between chest tube placement with fibrinolytic therapy and VATS when comparing hospital length of stay, days until afebrile, days of oxygen requirement, analgesic requirements or failure rates. Of the previously mentioned studies, two of them compared the costs of chest-tube placement with fibrinolytic therapy to VATS and found VATS to be significantly more costly. Those studies found that chest tube placement with fibrinolytic therapy represented a cost-savings of $2,300 - $4,100 [4, 15].

Based on cost information from our organization, chest tube placement with fibrinolytic therapy represented an average cost savings of approximately $6,900. These savings were based on hospital costs and professional charges. It should also be noted that in situations where a chest tube was placed in the PICU under sedation and did not involve the operating room, the cost-savings was even greater.

While complication rates were noted to be similar for both groups of patients, the complications observed in the VATS group did tend to be more severe, though one patient undergoing chest tube placement with fibrinolytic therapy did experience a severe bronchospasms that necessitated tracheal intubation. The most commonly observed complications in the VATS group was prolonged air leak, need for prolonged ventilatory support following procedure and wound infection [1, 4, 15, 16].

b. The timing of drainage, regardless of the intervention chosen, is an important consideration.

One study that looked at VATS done within 48 hours of admission versus VATS done after 48 hours found that those patients who underwent early VATS had a 4 day shorter length of stay [17]. Another study found that those patients who had surgery more than 4 days after their initial diagnosis had a significantly more complicated disease course [18].

c. Currently, tPA (tissue plasminogen activator) is the preferred debridement agent in the US [2].

One pediatric trial compared urokinase to saline, for use as a debriding agent, and found that urokinase significantly reduced the length of stay in patients with empyema [19].

Heparin was used in an animal model and was not found to be effective [20]. Streptokinase and urokinase were found to be equally effective in a study of adults [21]. While there are no studies directly comparing tPA to urokinase, of the three prospective studies that found VATS to be equally effective as fibrinolytic therapy, two compared VATS to urokinase and the other compared VATS to tPA. All of these studies achieved similar results, which would suggest that urokinase and tPA are comparable [1, 4, 15]. Currently, tPA is the only studied fibrinolytic agent that is commercially available within the United States.

d. Small-bore drains are recommended for routine use over large-bore drains

To date, there have been no randomized controlled trials designed to specifically address clinical outcomes of patients treated with differing size drains. Two large trials found no difference in efficacy of drainage between large-bore and small-bore drains [22, 23], but neither trial was designed to specifically answer the question of chest tube size. This finding was made on retrospective analysis. There has also been previously published data that support high success rates of drainage with small-bore drains [24].

For this reason, in addition to improved patient comfort, current adult guidelines for the management of empyema from the American Association for Thoracic Surgery and the British Thoracic Society both recommend the use of small-bore drains for the drainage of pleural fluid [9, 24]. Current pediatric guidelines from the British Thoracic Society recommend the use of small-bore catheters (including pigtail catheters) for drainage of pleural fluid [13]. Current guidelines from the American Pediatric Surgical Association do not specifically address catheter size.

It is our organization's practice to use a 12 Fr Thal-Quick chest tube. There are 2 methods to instill tPA through the chest tube. tPA can be injected directly into the tube using a small bore needle to puncture the tube. The needle should be inserted at an angle to the tube and a tegaderm can be used to cover the puncture site. Alternatively, a 3/8'' by 3/8' ECMO Circuit Connector can be placed between the Chest Tube and the Chest Tube Tubing. The ECMO Connector has a side port which allows installation of the tPA.

e. Fibrinolytic Frequency

There have been no studies to compare different fibrinolytic instillation protocols. Of the three studies done in pediatric patients that found VATS and chest tube with fibrinolytic therapy to be equally

effective, two of the study's protocols used urokinase that was instilled every 12 hours for 3 days [1, 15]. The other study protocol used tPA instilled every 24 hours for 3 total doses [4]. This study and the APSA guidelines used 4mg of tPA mixed into 40mL of sterile normal saline, which was then instilled through the catheter [2, 4].

It is our organization's practice to use tPA instilled every 24 hours, with a 1 hour dwell time, for 3 total doses.

f. Drain Removal

There have been no studies done to determine the optimal timing for chest tube removal. While US pediatric empyema guidelines do not mention specific criteria for when to remove a chest tube, the Infectious Diseases Society of America guidelines for the treatment of pediatric pneumonia recommend removal of the chest tube, after completion of fibrinolytic therapy, when drainage is less than 1 ml/kg/day, calculated over the previous 12 hours [11].

Of the three studies done in pediatric patients that found VATS and chest tube with fibrinolytic therapy to be equally effective, two of the study's protocols removed the chest tube when drainage was less than 40-60 ml in 24 hours [1, 15]. The other study protocol removed the chest tube when drainage was less than 1 ml/kg/day, calculated over the previous 12 hours [4]. Since these studies achieved similar results, either criteria for chest tube removal is considered appropriate.

g. Laboratory Evaluation of Pleural Fluid

Pleural fluid should be sent for culture and sensitivities to optimally guide antibiotic therapy. Pleural fluid cultures have been shown to be positive in 29-40% of patients with empyema [25, 26].

4. When to consider VATS

Of the three studies done in pediatric patients that found VATS and chest tube with fibrinolytic therapy to be equally effective, two of the study's protocols defined fibrinolytic failure as persistent fever four days after fibrinolytic therapy that was associated with a persistent fluid collection on chest US. Of these studies, one protocol called for salvage VATS [15] while the other protocol left the salvage therapy up to the attending physician [1]. The third study did not specify a salvage protocol in their study design. Since clinical parameters such as fever or persistent oxygen requirement can persist due to the severity of the underlying parenchymal disease, it is important that follow-up US be done to document a persistent fluid collection before failure of fibrinolytics is declared [2].

No studies have clearly established whether there is a difference between repeat attempts of fibrinolysis with tPA or proceeding to VATS when fibrinolytic failure has occurred, so additional courses of fibrinolysis with tPA may be appropriate, depending on the clinical scenario.

5. **Antibiotic Treatment**
    a. **Initial Empiric Therapy**

        Empiric therapy for the treatment of pneumonia with empyema should be with Ceftriaxone. Clindamycin or Vancomycin can be added if there is concern for MRSA. If cultures are positive, they should be used to tailor antibiotic therapy.

    b. **Length of Therapy**

        The length of antibiotic therapy in children with empyema after successfully undergoing fluid drainage has not been well studied. Current recommendations from the American Pediatric Surgical Association and the Infectious Diseases Society of America call for 2-4 weeks of continued antibiotic therapy, though the IDSA guidelines do state that some experts treat for approximately 10 days after fever resolution [2, 11]. British pediatric empyema guidelines recommend continued antibiotic therapy for 1-4 weeks after discharge [13].

        Of the three studies done in pediatric patients that found VATS and chest tube with fibrinolytic therapy to be equally effective, only one study discussed a discharge antibiotic regimen. That regimen was for at least 10 days of oral antibiotics that provided similar antimicrobial coverage as the IV antibiotic administered during the hospital stay [4].

6. **Discharge Criteria**
    a. **Patients who have undergone treatment for empyema may be discharged home if they are well appearing, tolerating good oral intake, are no longer requiring oxygen and have been afebrile for 24 hours.**

        Current recommendations from the American Pediatric Surgical Association state that fever is not necessarily a reason for continued hospitalization, as this can persist due to the severity of the underlying parenchymal disease. They state that signs of treatment failure include poor oral intake, continued oxygen requirement and evidence of continued fluid collection on chest imaging. They state that a patient who continues to have intermittent fever, but is otherwise doing well with good oral intake and no oxygen requirement can be discharged home as long as they do not have pleural disease that is causing atelectasis and lung trapping [2].

        Of the three studies done in pediatric patients that found VATS and chest tube with fibrinolytic therapy to be equally effective, one study

protocol stated children were eligible for discharge after being afebrile for 24 hours after drain removal [15], another discharged children after being afebrile for 24 hours on oral antibiotic therapy (patients were transitioned to oral antibiotics after being afebrile for 24 hours after chest tube removal) [1], and the final study required that patients be afebrile for 48 hours after chest tube removal [4].

Given the APSA recommendations and that one of the above studies deemed patients eligible for discharge after afebrile for 24 hours without any stated poor outcomes, 24 hours of the patient being afebrile is a reasonable criteria for discharge, so long as they are otherwise doing well.

7. Follow-up

a. Follow-up imaging

Local expert consensus recommends that these children have follow-up imaging at approximately 6-8 weeks post-discharge and that these children be followed until their chest x-ray findings normalize. One study of pediatric patients with empyema found that chest x-ray normalization will typically occur within 3-6 months of discharge [27].

1. Marhuenda, C., et al., *Urokinase versus VATS for treatment of empyema: a randomized multicenter clinical trial.* Pediatrics, 2014. **134**(5): p. e1301-7.
2. Islam, S., et al., *The diagnosis and management of empyema in children: a comprehensive review from the APSA Outcomes and Clinical Trials Committee.* J Pediatr Surg, 2012. **47**(11): p. 2101-10.
3. Chan, W., et al., *Empyema thoracis in children: a 26-year review of the Montreal Children's Hospital experience.* J Pediatr Surg, 1997. **32**(6): p. 870-2.
4. St Peter, S.D., et al., *Thoracoscopic decortication vs tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial.* J Pediatr Surg, 2009. **44**(1): p. 106-11; discussion 111.
5. King, S. and A. Thomson, *Radiological perspectives in empyema.* Br Med Bull, 2002. **61**: p. 203-14.
6. Jaffe, A., et al., *Role of routine computed tomography in paediatric pleural empyema.* Thorax, 2008. **63**(10): p. 897-902.
7. Brenner, D.J. and E.J. Hall, *Computed tomography--an increasing source of radiation exposure.* N Engl J Med, 2007. **357**(22): p. 2277-84.
8. Calder, A. and C.M. Owens, *Imaging of parapneumonic pleural effusions and empyema in children.* Pediatr Radiol, 2009. **39**(6): p. 527-37.
9. Shen, K.R., et al., *The American Association for Thoracic Surgery consensus guidelines for the management of empyema.* J Thorac Cardiovasc Surg, 2017. **153**(6): p. e129-e146.
10. Lamas-Pinheiro, R., et al., *Thoracoscopy in the management of pediatric empyemas.* Rev Port Pneumol (2006), 2016. **22**(3): p. 157-62.

11. Bradley, J.S., et al., *The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America.* Clin Infect Dis, 2011. **53**(7): p. e25-76.
12. Carter, E., et al., *Management of children with empyema: Pleural drainage is not always necessary.* Pediatr Pulmonol, 2010. **45**(5): p. 475-80.
13. Balfour-Lynn, I.M., et al., *BTS guidelines for the management of pleural infection in children.* Thorax, 2005. **60 Suppl 1**: p. i1-21.
14. Soares, P., et al., *Pediatric parapneumonic pleural effusions: experience in a university central hospital.* Rev Port Pneumol, 2009. **15**(2): p. 241-59.
15. Sonnappa, S., et al., *Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema.* Am J Respir Crit Care Med, 2006. **174**(2): p. 221-7.
16. Cobanoglu, U., et al., *Comparison of the methods of fibrinolysis by tube thoracostomy and thoracoscopic decortication in children with stage II and III empyema: a prospective randomized study.* Pediatr Rep, 2011. **3**(4): p. e29.
17. Padman, R., et al., *Parapneumonic effusion and empyema in children: retrospective review of the duPont experience.* Clin Pediatr (Phila), 2007. **46**(6): p. 518-22.
18. Kalfa, N., et al., *Thoracoscopy in pediatric pleural empyema: a prospective study of prognostic factors.* J Pediatr Surg, 2006. **41**(10): p. 1732-7.
19. Thomson, A.H., et al., *Randomised trial of intrapleural urokinase in the treatment of childhood empyema.* Thorax, 2002. **57**(4): p. 343-7.
20. Dikensoy, O., et al., *Intrapleural heparin or heparin combined with human recombinant DNase is not effective in the treatment of empyema in a rabbit model.* Respirology, 2006. **11**(6): p. 755-60.
21. Bouros, D., et al., *Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study.* Am J Respir Crit Care Med, 1997. **155**(1): p. 291-5.
22. Rahman, N.M., et al., *Intrapleural use of tissue plasminogen activator and DNase in pleural infection.* N Engl J Med, 2011. **365**(6): p. 518-26.
23. Maskell, N.A., et al., *U.K. Controlled trial of intrapleural streptokinase for pleural infection.* N Engl J Med, 2005. **352**(9): p. 865-74.
24. Davies, H.E., et al., *Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010.* Thorax, 2010. **65 Suppl 2**: p. ii41-53.
25. Angurana, S.K., et al., *Pediatric empyema thoracis: What has changed over a decade?* J Trop Pediatr, 2018.
26. Gonzalez, K.W., et al., *Antibiotic utilization based on primary treatment of pediatric empyema.* J Surg Res, 2015. **196**(2): p. 320-4.
27. Chan, P.W., et al., *Treatment of pleural empyema.* J Paediatr Child Health, 2000. **36**(4): p. 375-7.

This guideline is intended to assist providers in decision making by providing the current state of evidence and recommendations for the management of empyema. This guideline is not meant to replace clinical judgement and will not be appropriate for all cases of empyema.

Empyema Clinical Guideline Team:

Marty Knott, DO (Team Leader) – Pediatric Surgery
JoAnn Bradden, RN – 5-North Nursing
Matthew Carroll, MD – Hospital Medicine
Michelle Crawford, PharmD, BCPS – Antimicrobial Stewardship Program
Marc Mazade, MD – Infectious Disease
Adeka McIntosh, MD – Interventional Radiology
Karen Schultz, MD – Pulmonary Medicine
Phillip Scott, MD – Hospital Medicine
William Stigall, MD – Pediatric Critical Care

A special thanks to the Schwarz Library for their assistance with literature searches and to our finance department for their assistance with pulling financial data.

Approved by Clinical Excellence Committee: April 17, 2019

Reviewed and Renewed by Clinical Excellence Committee: October 2022

Due for review by Clinical Excellence Committee on or before: October 2025