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Review Articles

The diagnosis and management of empyema in children: a comprehensive review from the APSA Outcomes and Clinical Trials Committee

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Abstract The aim of this study is to review the current evidence on the diagnosis and management of empyema. The American Pediatric Surgical Association Outcomes and Clinical Trials Committee compiled 8 questions to address. A comprehensive review was performed on each topic. Topics included the distinction between parapneumonic effusion and empyema, the optimal imaging modality in evaluating pleural space disease, when and how pleural fluid should be managed, the first treatment option and optimal timing in the management of empyema, the optimal chemical debridement agent for empyema, therapeutic options if chemical debridement fails, therapy for parenchymal abscess or necrotizing pneumonia and duration of antibiotic therapy after an intervention. The evidence was graded for each topic to provide grade of recommendation where appropriate.

Although overall rates of bacterial pneumonia have been declining in children, the incidence of complications such as parapneumonic effusions and empyema has increased [1]. In

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the United States, pneumonia in children occurs at an estimated rate of 30 to 40 per 100,000 [2]. In children younger than 2 years, the incidence of empyema doubled over the span of a decade, increasing from 3.5 per 100,000 in 1996 to 1998 to 7 per 100,000 in 2005 to 2007. Similarly in patients between 2 to 4 years age, empyema rates nearly tripled from 3.7 to 100,000 to 10.3 to 100,000 during the same period [3]. While pediatric empyema is less serious compared to adults where mortality can approach 20%, it still poses a considerable burden on hospitals and families. Different treatment strategies continue to generate controversy [4]. Much of the data used in pediatric surgical practice are derived from adult studies [5]. However, recent studies have focused on the management of empyema specifically in children, thus prompting this review from the APSA Outcomes and Clinical Trials Committee [5,6]. In this review, we will address some of the most germane issues to pediatric surgeons and assess the available evidence, providing recommendations and suggestions when appropriate. Adult data will also be considered where appropriate considering the paucity of pediatric information available.

1. Methods

The APSA Outcomes and Clinical Trials Committee approved 8 questions that are salient to the management of pediatric empyema to address for this review. Literature searches were performed in English using Medline, PubMed, CINAHL, EMBASE and pertinent Cochrane reviews. Search terms were chosen by the author assigned to the specific section by utilizing multiple terms relevant to the topic addressed. Reference lists of relevant manuscripts were used to identify other relevant contributions. Studies were grouped into levels of evidence based on established guidelines to grade the recommendations in each section. (Table 1). Studies in children and adults were graded using the same scale.

Table 1 Grading classification for the levels of evidence and grades of recommendation according to the Oxford Centre for Evidence-based Medicine Levels of Evidence, March 2009

Classes of evidence	Grades of recommendation
I Systematic review of RCT's or with one RCT with narrow CI	A - Consistent Level 1 Studies
II Cohort studies, low quality RCT's, outcomes research	B - Consistent Level 2 or 3 studies or extrapolation from Level I studies
III Case–control studies	C - Level 4 studies or extrapolations from Level 2 or 3 studies
IV Case series	D - Level 5 evidence or inconsistent or inconclusive studies
V Expert opinion	

(www.cebm.net). RCT, randomized controlled trial. C; –/ confidence interval.

The questions that are addressed are:

1. Should the distinction between parapneumonic effusion and empyema affect clinical decision making?
2. What is the optimal imaging modality in evaluating pleural space disease?
3. When and how should pleural fluid be managed?
4. What is the first treatment option and optimal timing in the management of empyema?
5. What is the optimal chemical debridement agent for empyema?
6. What therapeutic options exist if chemical debridement fails?
7. What is the management for parenchymal abscess or necrotizing pneumonia?
8. What is the duration of antibiotic therapy after an intervention?

1.1. Should the distinction between "parapneumonic effusion" and "empyema" affect clinical decision-making?

Parapneumonic effusions (PPE) or empyema complicate pediatric pneumonia in 28–53% of cases [7,8]. Although the natural progression of these conditions has not been studied in any systematic fashion, parapneumonic pleural disease is classically thought to occur in 3 to 4 stages of increasing complexity [5,6,9].

1. The pre-collection stage occurs when pneumonia is associated with pleuritis and inflammation.
2. The exudative stage or simple PPE is characterized by clear, free-flowing pleural fluid with low white cell count. This may or may not progress on to the next stages.
3. In the fibrinopurulent stage or complicated PPE, there is deposition of fibrin and purulent material in the pleural space, correlating with an increase in the cell count of the parapneumonic fluid. Septations and fibrin strands appear. Purulent material may be present within the pleural space.
4. When the organizational stage is reached, a thick pleural peel is established, which may entrap the lung and result in a chronic restrictive pattern of lung disease. This stage is rare in the modern era, especially in children.

Through the course of disease progression, glucose decreases, pH decreases and lactate dehydrogenase rises in the pleural fluid. The Light criteria for defining complicated PPE include pH <7.2, lactate dehydrogenase >1000 U; glucose <40 mg/dL; or <25% blood glucose, Gram stain, or culture positive and with loculations or septations proven with imaging [10]. In a 1995 review, Light proposed a more

detailed classification for pleural fluid collections secondary to pneumonia which considered radiologic and pleural fluid characteristics. This scheme used 7 different classes from non significant parapneumonic effusions to a complex empyema with associated recommendations on therapy escalating from observation to thoracoscopic decortication [11]. Similarly, a consensus statement from the American College of Chest Physicians in 2000 reviewed the available literature and concluded that there was a low level of evidence available, and noted that poor outcome may correlate with radiologic and pleural fluid analysis therefore requiring more interventional therapy as the stage of effusion was higher [12]. Retrospective data suggest that pleural fluid pH, glucose, and LDH pleural/serum ratio are associated with a prolonged fever suggesting worse disease [13]. Multivariate logistic analysis of a retrospective dataset found that pH (<7.27) in pleural fluid was the only significant factor for the formation of fibrin with/without septations [14]. Similarly, a pleural fluid pH less than 7.1 has been found to result in a 6 fold increase in the likelihood of surgical intervention based on retrospective data [15]. Systemic antibiotic therapy for greater than 48 hours before tap has been shown to result in significantly lower culture yield but without affecting the biochemistry of the fluid [16]. While these criteria document the physiologic progression of disease, the clinical relevance of the chemical analysis of pleural fluid is diminishing. In practice, once pleural space debris causes symptoms and requires removal, drainage can be achieved based on the nature of the debris.

1.1.1. Summary

The classifications of parapneumonic effusion or empyema may be helpful in understanding the pathophysiology of disease. However, there are no data that correlate these stages with specific management strategies. The evidence for the classifications is weak. The factors that lead to selection of management strategies in contemporary practice are addressed below.

1.2. What is the optimal imaging modality in evaluating pleural space disease?

Imaging plays a central role in the diagnosis and management of pleural space disease. The principal modalities are chest radiographs (CXR), ultrasound (US), and computed tomography (CT) [17,18]. The use of magnetic resonance imaging has not been evaluated in pediatric empyema and will not be discussed.

1.2.1. Chest radiographs

It is difficult to distinguish between parenchymal consolidation and pleural fluid using plain radiographs [18]. In a retrospective review of over 300 adult patients, CXR missed all effusions that were significant enough to warrant drainage by subsequent CT scans [19]. Decubitus films may be helpful to distinguish between free flowing PPE vs loculated collections [18]. Therefore, other methods of imaging may be required [17].

1.2.2. Ultrasonography

Ultrasound is an imaging modality that is portable, relatively inexpensive and involves no radiation exposure. It is utilized to guide percutaneous drainage and catheter placement [20,21]. Some authors suggest that US is superior to CT in the identification of pleural debris or loculations [17,22]. US can reliably differentiate between parenchymal and pleural based processes [5]. In a post hoc review of a prospective trial comparing fibrinolysis to operative debridement in children, 31 patients in whom both CT and US were performed for the evaluation of the effusion were analyzed. The authors found that CT provided no advantage over US in most cases [1]. Two independent series reviewed the implementation of an algorithm for managing complicated pneumonia in children, and both demonstrated a significant reduction in length of stay following implementation. Furthermore, the authors noted a significant decrease in the use of CT and an increase in US utilization without an increase in the rate of operative management or pleural drainage [23,24]. A small retrospective review comparing US and CT found that CT had no advantage in most cases and suggested that CT should be used in complex cases only, such as patients undergoing surgery or considered to have parenchymal abscesses or broncho-pleural fistulae [22]. However, the limited 24-hour availability of US may be problematic in some hospital systems. Furthermore, the quality of US imaging is operator dependent compared to CT at many institutions, which may further limit its clinical utility for directing treatment.

1.2.3. Computed tomography

Recent data regarding the potential increase in long-term cancer risk from cumulative CT scan exposure have raised the level of concern regarding routine CT use [25]. A CT scan of the chest can be performed effectively with the use of automatic dose modulation software while limiting the radiation dose in modern scanners [17]. In pleural space disease, CT with intravenous contrast can differentiate between parenchymal and pleural processes, identifying pleural thickening and loculations [22]. Computed tomography was found to be inferior to US at demonstrating fibrin strands or septations within the pleural fluid [17]. Neither CT nor US is completely reliable in differentiating the specific stages of parapneumonic disease as outlined in our first question (see I) [1,17,22]. Consensus statements are also clear in their recommendations of performing CT only when needed, such as preoperative planning in some cases [5,6].

1.2.4. Summary

US should be the initial and primary imaging modality used to evaluate the pleural space in children with suspected pleural space disease on CXR. Its ability to identify

loculations and solid components of the inflammatory process can help direct management. Computed tomography should be reserved for more complicated cases such as those where characterization of the extent of parenchymal disease and/or the presence and location of lung abscess may impact surgical decision-making, and for cases where the quality of US is inadequate owing to body habitus or other patient characteristics (grade C recommendation).

1.3. When and how should pleural fluid be managed?

The literature cites 3 criteria to determine whether drainage of PPE is necessary: effusion size, presence of symptoms, and evidence of loculations on imaging.

1.3.1. Size

The size classification for effusions is arbitrary and mostly based on plain chest radiographs in adult patients. On decubitus chest x-rays, small effusions are defined as having <1 cm rim of fluid, moderate effusions have 1 to 2 cm rim, and large effusions have >2 cm rim. On upright chest radiographs, small effusions have less than one-fourth of the thorax opacified, moderate effusions have more than one-fourth but less than one-half of the thorax opacified, and large effusions occupy greater than one-half of the thorax [26]. Mediastinal shift is considered to be a finding that may be associated with compromised cardio-respiratory function. Adult data suggest that effusions that are larger than 40% to 50% of the thorax seldom resolve without drainage, although this may not be true for the pediatric population [19]. A recently published 12-year retrospective study in children suggests that small and most moderately sized effusions may be effectively be managed without drainage without an increase in the length of stay or other complications [26]. Larger effusions in children tended to be symptomatic and therefore required a procedure based on symptoms, not size alone [26].

1.3.2. Symptoms

Progression of symptoms or lack or response to medical therapy may provide impetus to evaluate for treatable pleural space disease. Symptoms may include fevers, tachypnea, and increasing oxygen requirement. The size of effusion typically correlates to the presence of symptoms [6]. A retrospective case series in children found respiratory distress on presentation was related to prolonged stay and a higher likelihood for intervention [27].

1.3.3. Loculations

Loculations or septations on imaging represent fibrin deposition in the pleural space. The presence of loculations has a moderate correlation with purulence and typically requires intervention in addition to antibiotics [17,27].

Options to drain PPE include thoracentesis (single vs multiple); tube thoracostomy alone; tube thoracostomy with chemical/enzymatic debridement, or video-assisted thoracoscopic surgery (VATS) debridement. A prospective, non-randomized series compared treating children with repeated US guided needle aspirations to tube thoracostomy [28]. Thirty-five patients had alternate day thoracentesis for an average of 2.4 drainage procedures per patient and had similar length of stay to patients managed with a chest tube, although 5 patients failed to respond in each group and underwent either fibrinolysis or surgery [28]. While this approach may be reasonable in an older child who could tolerate the procedure with a local anesthetic and sedation, it would likely not be appropriate in younger children. Furthermore, repeated drainage procedures may not represent a cost-effective management strategy when considering the number of sedation procedures required for treatment as outlined in the aforementioned study.

The British Thoracic Society guidelines recommend a chest tube for cases in which the first thoracentesis fails to adequately drain the effusion in order to avoid multiple attempts [5]. A retrospective series compared 33 children who underwent chest tube placement on the basis of effusion size and/or thoracentesis fluid analysis versus 32 who were treated conservatively with chest tube placement only for progressive symptoms or mediastinal shift [29]. The authors noted no difference in the length of stay and recommended restricting the use of chest tubes. A single multicenter prospective trial in adults have studied the optimal chest tube size for the use of fibrinolytics [30]. Among 405 adult patients, 266 had chest tube smaller than 14 French placed, while 139 had larger tubes placed. There was no difference in mortality or ability to drain the fluid between the smaller and larger tubes. However, pain scores were improved in the patients with the smaller wire-guided tubes. Smaller caliber tubes did not hinder the use of fibrinolytics. In a retrospective series, 20 children treated with standard chest tubes were compared to 12 treated with pigtail tubes and no differences were found [31].

1.3.4. Summary

Radiographic and clinical parameters may guide the decision for intervention in PPE. Fluid evacuation should be considered in large effusions, effusions associated with loculations and in moderate effusions associated with symptoms that are worsening or not improving (grade C recommendation). Free-flowing PPE may be drained by a single thoracentesis in an older child. Repeated thoracentesis is not recommended in younger children. Small-bore tubes (<14F) should be used whenever possible, even for loculated effusions as they have been shown to be more effective when performing fibrinolysis (grade C recommendation).

1.4. What is the first treatment option and optimal timing in the management of empyema?

Empyema is diagnosed by identifying solid components in the pleural fluid or if pus is identified during thoracentesis

or tube placement. Historically, the definitive management for empyema has been surgical debridement. In the early part of the last decade, the minimally invasive approach (VATS) became the gold standard for operative management of fibropurulent pleural space disease [32-37]. VATS has resulted in earlier and more complete resolution of empyema than chest tube drainage alone in both retrospective and prospective studies translating in shorter hospitalization with primary VATS [14,15,38-41]. A retrospective series of 89 children undergoing primary VATS found a 12% risk of a subsequent procedure to address ongoing disease or a complication [42]. However, the superiority of operative mechanical debridement as a definitive management strategy has been increasingly challenged by chemical debridement.

Chemical debridement with fibrinolytics takes advantage of the pathophysiology of empyema formation. When the pleural space becomes infected, the ensuing inflammatory reaction is associated with fibrin deposition and decreased fibrinolytic activity. This creates a procoagulant environment leading to the development of solid material in the form of septations or loculations [43]. A fibrinolytic agent breaks down fibrin. The common examples are urokinase, streptokinase and tissue plasminogen activator (tPA). Since fibrin is a predominant component of the extracellular matrix upon which septations and solid debris form, instillation of a fibrinolytic agent to liquefy pleural space disease has been shown to be effective in promoting resolution of empyema in multiple studies [39,40,44-63].

Fibrinolysis has been shown to be superior to chest tube drainage alone in retrospective and prospective studies, by both direct comparison and when used in patients who failed chest tube drainage only [44-46,50,53-55,58,61,63]. One small retrospective series found no benefit to streptokinase over tube thoracostomy alone [64]. One prospective randomized trial in adult patients with empyema comparing fibrinolysis with streptokinase to chest tube drainage alone found an improved success rate for resolution of empyema in those patients treated with streptokinase (87.7% vs. 67%; $P < .05$) [46]. Furthermore, treatment of empyema with fibrinolytics instilled through an indwelling chest tube has been shown to be more cost-effective than treatment with a chest tube alone [65].

The timing of intervention, by fibrinolysis or VATS, is an important consideration in the treatment of empyema. A retrospective series in children with empyema documented that VATS performed within 48 hours of diagnosis reduced hospital stay by 4 days on average [14]. Another retrospective study showed a delay between diagnosis and surgery of more than 4 days was significantly correlated with more frequent surgical difficulties, longer operative time, more postoperative fever, longer drainage time, longer hospitalization, and more postoperative complications [66]. Similarly, a retrospective comparison in adults found that patients with empyema have a more efficient course if treated with primary VATS compared tube thoracostomy alone with VATS reserved for failure [67]. In a prospective trial of 18 children with empyema, 10 patients who underwent VATS upon diagnosis were compared to 8 initially managed with chest tube drainage [38]. Of those initially managed nonoperatively, the effusion failed to resolve in 7 patients who were then treated successfully with instillation of tPA into the chest tube for up to 5 days. The protracted staggered pathway resulted in an extra week in the hospital for the patients treated initially with tube thoracostomy compared to those treated with definitive mechanical debridement upon diagnosis. This study underscores the importance of definitive management upon diagnosis of empyema without an initial attempt of chest tube drainage alone.

Two prospective, randomized trials have been conducted independently comparing fibrinolysis to VATS upon diagnosis of empyema in children [68,69]. One was performed in England and the other in the United States. Both studies compared the installation of 3 intra-thoracic doses of fibrinolytic agents to VATS as the initial therapy for empyema. Both studies used intra-institutional retrospective data on the 2 therapies to calculate the sample size, which were 60 and 36 patients respectively. The first fibrinolytic dose was given upon diagnosis and/or chest tube placement followed by 2 additional doses in 24-hour increments to complete the course over a 48-hour period. One study used tPA with a one-hour dwell time and the other used urokinase with a four-hour dwell time. The primary outcome variable for both studies was length of post-intervention hospitalization. The results were highly concordant with both documenting no difference in length of hospitalization. The common parameters between the 2 studies are outlined in Table 2. The study conducted in the United States found no difference in days of tube drainage, days of fever, doses of analgesics or oxygen requirements. The raw numbers were similar between the 2 studies. Due to the nearly identical results, it can be surmised that longer clamp or dwell time may not pose a treatment advantage over shorter dwell times, although a direct comparative analysis has not yet been reported. Both studies documented significantly higher costs or hospital charges with VATS. The studies utilized an intention-to-treat analysis so the length of stay and total charges included the patients who failed fibrinolysis and were subsequently treated with VATS. The failure rate for

Table 2 Common variables reported between the 2 prospective trials comparing fibrinolysis to VATS in children [50,51]

Study	Sonnapa 2006			St. Peter 2009		
Arm	Urokinase	VATS	*P*	tPA	VATS	*P*
Length of stay (d)	6	6	.33	6.8	6.9	.96
Charges *	9.1K	11.3K	<.001	7.5K	11.6K	.01
Failure rate	16.6%			16.6%		

* Charges are in thousands of British pounds for Sonnapa and thousands of US dollars for St Peter.

fibrinolysis was 16.6% in both studies. The failure rate was similar to previous studies investigating the utility of fibrinolysis [46,54,59,60,62,65,68,70]. An example of a first-line fibrinolysis therapeutic approach is outlined Fig. A similar algorithm has been proposed based on a review of the literature [71]. However, the agent, dosage, concentration, dwell time, interval and total doses are all parameters that have not been proven with comparative data and are subject for future investigation.

When comparing fibrinolysis to VATS, the burden to the patient should be considered given that one therapy is a nonoperative procedure requiring a single sedation and the other is a surgical procedure under general anesthesia. The only current systematic review of randomized trials in the local treatment of pediatric empyema, albeit simply a review of the 2 trials, concludes that non-operative management should be the first line of therapy if feasible [72]. It is important to note that the available evidence would suggest that VATS is neither superior or inferior to fibrinolytic therapy as a primary treatment modality in assisting in recovery. Therefore, if performed at the time of diagnosis, VATS remains an equivalent option to facilitate early recovery when fibrinolysis is not feasible given hospital and physician resources. This may be particularly relevant if an anesthetic is required for tube placement for fibrinolysis.

1.4.1. Summary

Once an effusion is diagnosed as empyema, definitive management should be initiated with mechanical or chemical debridement (grade B recommendation). Chemical and mechanical debridements have been shown to have equivalent outcomes in 2 prospective trials. Since chemical debridement does not require an operation, it is reasonable to utilize chemical debridement as first line therapy. Operative management should be reserved for patients who fail to respond to chemical debridement if healthcare resources allow for such management (grade A recommendation).

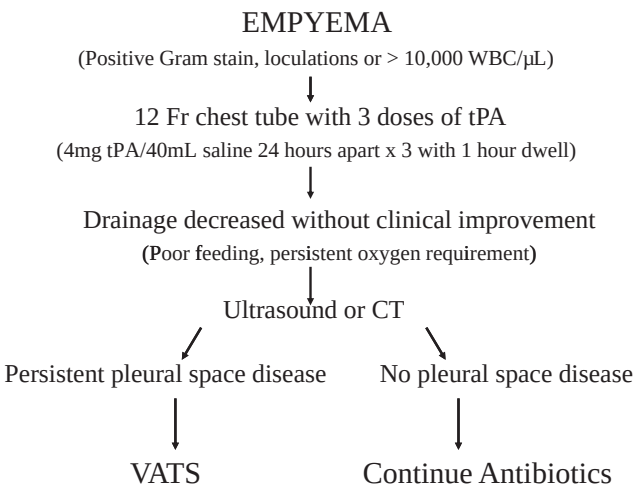

Fig. Treatment algorithm for empyema in children [60,65].

1.5. What is the best agent for chemical debridement?

1.5.1. Fibrinolytics versus saline

One pediatric trial, randomizing 60 patients to urokinase versus saline, found a significant reduction in length of stay by 2 days for fibrinolysis [58]. In this study, there was no significant difference in the percentage of patients who failed therapy and were subsequently treated VATS as there were 2 failures in the urokinase group and 2 in the saline group.

There are 5 prospective, Cochrane grade A trials in the adult literature comparing fibrinolytic to saline, which are summarized in Table 3 [73-77]. The initial 4 trials found a reduced risk of treatment failure or requirement for surgery in the fibrinolysis group [73-76]. In a subsequent larger multicenter trial comparing streptokinase to normal saline in 427 patients, no differences in recovery were recorded [73-76]. These 5 studies have been summarized in 2 separate meta-analyses, one in 2006 and the other is the most recent Cochrane update in 2008, which found the pooled risk ratio for surgery following fibrinolytic therapy to be 0.53 (95% CI, 0.28-1.02) and 0.71 (95% CI, 0.50-0.99), respectively [78,79]. The differing risks resulted from different relative weights given for the trials in the pooled analysis. All but one trial showed benefit of fibrinolytic therapy. Suggested reasons for the discrepancy found in the negative trial include lack of protocol control, surgical referral based on clinical judgment, and the central randomization sequence included the mailing of streptokinase to the participating centers which delayed fibrinolytic treatment [78]. Another consideration was the inclusion of patients with acidic pleural fluid and those with bacteria in the pleural fluid, which may not capture the group most likely to benefit from fibrinolysis who have solid material or loculations within the pleural space. The 2008 Cochrane review included subgroup analysis leading to the conclusion that there is an overall benefit to the use of fibrinolytics in the group with loculations (pooled risk ratio, 0.63; 95% CI, 0.46-0.85).

1.5.2. Comparison of fibrinolytics

One prospective trial in 30 children found no difference between once and twice a day dosing of streptokinase [62]. Germaine to discussion above, the success rate was over 90% in both group. In comparing agents for chemical debridement, heparin has been attempted in an animal model without success [80]. In a rabbit model, there was no difference in pus viscosity after treatment with streptokinase or urokinase [81]. One prospective randomized trial in 50 adults with empyema comparing streptokinase to urokinase found no difference in resolution of disease. The authors conclude that urokinase would be favored over streptokinase as severe allergic reactions to streptokinase was seen in 2 patients [82]. We do not have good data comparing tPA to urokinase. However, the 2 prospective trials that showed fibrinolysis to be equal to VATS used urokinase in one and tPA in the other [65,68]. The fact that nearly identical clinical outcomes were recorded in the fibrinolysis arms of the 2 studies suggests that they are likely to

Table 3 Summary of adult empyema trials comparing chemical debridement with a fibrinolytic agent to saline alone

	N	Agent	Failure fibrinolysis	Failure saline	Risk ratio (95% CI)
Davies 1999	24	Streptokinase	0%	25%	0.14 (0.01-2.50)
Bouros 1999	31	Urokinase	13.3%	37.5%	0.36 (0.08-1.50)
Tuncozgur 2001	49	Urokinase	29.2%	60.0%	0.49 (0.24-0.98)
Diacon 2004	44	Streptokinase	13.6%	45.5%	0.30 (0.10-0.94)
Maskell 2005	454	Streptokinase	15.5%	14.8%	1.07 (0.68-1.69)

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) [59,60].

be equivalent. However, urokinase is no longer available in the United States, and subsequently tPA has become the most commonly used agent for pleural space disease [83].

1.5.3. Deoxyribonuclease

Deoxyribonuclease (DNase) is a mucolytic agent that may increase the effectiveness of non-operative pleural space debridement. When added to streptokinase in an in vitro study, DNase resulted in superior dissolution of human pus samples compared to streptokinase alone [84]. In a rabbit model of empyema, DNase combined with streptokinase, was found to significantly reduce pus viscosity compared to either urokinase or streptokinase alone [81]. In a rabbit model, DNase added to tPA was superior to either tPA, DNase or saline alone [85]. A case was reported of successful salvage therapy with the addition of DNase after failure of streptokinase alone [86].

While there are no comparative studies in children, one prospective trial was conducted in England on adult patients with empyema to investigate the role of DNase [87]. The 4 treatment groups included placebo, tPA only, DNase only and a combination of tPA and DNase. The primary outcome was decrease in opacity on plain films between days 1 and 7, which demonstrated significantly greater clearance with the mix of tPA and DNase ($P = 0.005$). However, this variable is of limited clinical relevance. There was a significantly decreased length of stay with tPA/DNase (11.8 ± 9.4 days) compared to placebo (16.5 ± 22.8 days) ($P = .006$). Furthermore, the percentages of surgical referrals resulting from failed medical therapy also trended in the same direction with 39% (18/46) failure with DNase, 16% (8/51) with placebo, 6% (3/48) with tPA, and 4% (2/48) with tPA/DNase. The results of the study suggests that DNase alone is a poor fibrinolytic but the combination of tPA and DNase is superior with improved clearance on plain films and possible shorter length of stay with a similar failure rate to tPA.

The type of DNase used in the study was dornase alpha or Pulmozyme (Roche, Basel, Switzerland), which is a mucolytic commonly used via intranasal and intratracheal routes in patients with cystic fibrosis or ventilator dependence and is readily available in most pediatric hospitals. However, it is not currently approved for intrapleural use in the United States. Similarly, a DNase and streptokinase combination called varidase is also not available in the United States.

1.5.4. Summary

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 (grade B recommendation). Currently, tPA is the only studied fibrinolytic available in the United States. DNase may be advantageous when added to fibrinolytics in adults (grade C recommendation).

1.6. When should VATS be considered after chemical debridement?

After completion of fibrinolysis, the chest tube is allowed to drain until the output decreases. In both prospective trials comparing VATS to fibrinolysis in pediatric patients, acceptable drainage for removal was 1 mL/kg per day or less, which can be calculated over the most recent 12 hours [68,69]. In the larger trial, failure of fibrinolysis was specifically defined as persistent fever of greater than 38.0°C or 100°F at 4 days after completion of therapy [65]. However, clinical parameters can be misleading since the persistence of fever or oxygen requirements may be due entirely to the severity of parenchymal disease, particularly in the face of substantial pulmonary necrosis or abscess. Therefore, the algorithm outlined in Fig. calls for an imaging modality to prove the presence of persistent solid material within the pleural space that is independent from the parenchyma. In the persistently ill child who has been treated with fibrinolysis, imaging documents whether debridement of the pleural space is satisfactory or not. Persistent illness is often accompanied by poor eating and ongoing oxygen requirement. Given that patients will continue on antibiotics for a protracted course regardless, the patient with fever who otherwise is eating and doing well on room air should be able to be discharged provided there is not pleural space disease to cause atelectasis and lung trapping.

1.6.1. Summary

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 (grade D recommendation).

1.7. What is the management for parenchymal abscess or necrotizing pneumonia?

In most patients who develop a lung abscess concomitant with pneumonia and empyema, the abscess arises in previously normal lung and may contribute to lack of clinical response. Patients with an abscess that is associated with an underlying anomaly such as a congenital pulmonary airway malformation are a distinct population from this group and resection should be considered after resolution of infection.

In a patient who has a lack of response to therapy, a CT should be considered to assess for lung abscess or necrosis. If a parenchymal abscess exists, it can be treated to resolution with antibiotics alone [88,89]. If the lesion is peripheral and not associated with communication with the airway, then CT or US guided drainage or catheter placement is feasible [90-92]. A small retrospective series suggests that drainage shortens hospital stay and facilitates earlier recovery [93]. Operative therapy is rarely required.

Lung necrosis represents the worst form of parenchymal disease and cannot be effectively treated by any means of pleural debridement. Although there are not published data informing the choice of treatment for this specific condition, it would seem prudent to treat these patients with ongoing antimicrobial therapy and no operation. If an operation was performed in the face of substantial necrosis the risks of air leak, bronchopleural fistula or uncontrollable bleeding are substantial.

The extent and severity of parenchymal disease relative to the pleural space disease is an important consideration to determine the primary source of illness and to direct care both before and after addressing the empyema. If diffuse necrosis can be recognized before embarking on definitive management for concomitant pleural space disease it would likely be better to begin with non-operative management. In the persistently ill patient after fibrinolyis, the source of illness may be entirely or mostly parenchymal in which case continuing antibiotics is likely a safer course than mechanically manipulating the attenuated lung.

1.7.1. Summary

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 (grade D recommendation).

1.8. What is the duration of antibiotic therapy after an intervention?

As discussed above, the optimal treatment of empyema rests with the ability to completely debride or clear the pleural space of debris to allow for adequate expansion of the lung parenchyma. This becomes the key variable in determining the length of antimicrobial treatment; however, the course may also be influenced by the pathogen. The length of antimicrobial therapy after completion of pleural treatment has not been reliably studied in children. Therefore, the standing recommendation is to continue therapy for 2 to 4 weeks. The most recent expert recommendation from consensus guidelines on the treatment of community acquired pneumonia is to continue treatment for approximately 10 days after resolution of fever in children treated for parapneumonic effusion or empyema [6].

1.8.1. Summary

Therapy should continue a minimum of 10 days after resolution of fever (grade D recommendation).

2. Summary

This review summarizes the current state of knowledge regarding the management of parapneumonic effusion and empyema. Ultrasound should be the initial and primary imaging modality with CT reserved for more complicated cases such as determination of parenchymal disease and lung abscess (grade C). Pleural space fluid should be considered for evacuation with large effusions, effusions associated with loculations, and in moderate sized effusions in patients who fail to progress or have worsening symptoms (grade C). A small-bore chest tube (<14F) should be used because it causes less pain and is effective with fibrinolytics (grade C). Two prospective trials have shown equivalence between chemical and mechanical debridement. Since chemical debridement offers non-operative management with decreased resource utilization compared to VATS, chemical debridement should be first line therapy when healthcare resources allow (grade A). Definitive management with either should be initiated as soon as empyema is diagnosed. (grade B). After fibrinolysis, if a patient is persistently ill after the chest tube drainage is diminished and imaging proves substantial pleural space disease, VATS should be considered. (grade D) Parenchymal abscess and lung necrosis should be managed non-operatively. (grade D). Antibiotic therapy should continue for at least 10 days after resolution of fever. (grade D).

Potential areas for future investigation include prospective studies to clarify the relative indication of US and CT in the algorithm of empyema. The addition of DNase during chemical debridement should be studied in children. Larger prospective studies are needed to identify risk factors associated with patients who fail fibrinolytic therapy and may benefit from primary mechanical debridement. In addition, prospective studies on dosages, dwell times, and length of non-operative management after fibrinolysis in the patients with persistent illness may identify which patients require VATS after chemical debridement.

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