Establishing Equipoise: National Survey of the Treatment of Pediatric Para-Pneumonic Effusion and Empyema

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Abstract

Background: Despite six randomized trials of various treatments for pediatric para-pneumonic effusion (PPE), management approaches differ. The purpose of this study was to gain insight into opinions on PPE treatment with the goal of designing a definitive trial to generate consensus intervention guidelines.

Methods: To evaluate physician opinions regarding PPE management, we developed a survey based on input from a nationwide, multi-disciplinary advisory group that established content validity. The survey was disseminated broadly to six pediatric medicine and interventional radiology groups. Descriptive and χ^2 statistics were calculated.

Results: There were 741 respondents (response rate 13.1%), of whom 52.2% were surgeons, 15.2% hospitalists, 14.2% pulmonologists, 12.4% intensivists, and 6.0% interventional radiologists. Nearly all respondents (97.3%) reported caring primarily for pediatric patients. Eighty percent reported no written institutional treatment guidelines. Nearly all (90.3%) agreed that patients require antibiotics, but there was disagreement regarding their duration. Respondents also were split as to how often PPE required drainage. There were multiple absolute indications for drainage, including mediastinal shift on chest radiograph (67.2%) and loculations on imaging (47.7%). There were substantial differences in the preferred first-line methods of drainage based on the treating physician's specialty, with surgeons preferring tube thoracostomy and a fibrinolytic agent (42.0%) or video-assisted thoracoscopic surgery (41.6%), whereas interventional radiologists preferred either a tube thoracostomy (46.4%) or a tube thoracostomy with a fibrinolytic agent (39.3%) ($p < 0.001$). A large majority (75.3%) believed that the published evidence does not identify the optimal intervention.

Conclusions: There is a lack of consensus regarding the optimal treatment of PPE. Respondents believed the published evidence is inconclusive and were willing to participate in a prospective trial. These findings will help inform the design of a randomized, pragmatic clinical trial to optimize PPE management.

Keywords: chest surgery; empyema; pneumonia

IN 2011, there were more than 1.1 million hospitalizations in the United States for which the principal diagnosis was pneumonia [1]. Outside of the birth hospitalization, pneumonia is the most common reason for hospital admission in children younger than 18 years, accounting for 167,600 admissions in 2009, with medical costs estimated at more than \$1 billion [1,2].

Pneumonia usually is defined as the presence of lower respiratory tract infection and associated inflammation,

which may manifest as systemic symptoms such as fevers, chills, leukocytosis, or leukopenia coupled with evidence of an acute respiratory illness, including cough, sputum production, chest pain, dyspnea, tachypnea, an abnormal lung examination, or, in severe cases, respiratory failure [3–5]. A para-pneumonic effusion (PPE) is a pleural effusion secondary to pneumonia or a lung abscess [6]. Pediatric PPE has an estimated incidence of 3.3 per 100,000 [7]. Although these effusions frequently have a three-stage natural history, which

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may be helpful to understand pathophysiology, reports suggest that these stages have limited value for influencing treatment decisions [6]. Stage 1 is characterized by fluid accumulation in the pleural space and is termed the “exudative phase.” Stage 2 is called the “fibropurulent phase” and is marked by adhesion and loculation formation. Stage 3 is defined by the formation of an inelastic peel around the lung and is referred to as the “organizational phase.” Stages 2 and 3 PPE are, by definition, infected [6,8]. Roughly 20%–40% of all patients with pneumonia have an associated PPE, whereas 1%–2% of pediatric patients with a diagnosis of pneumonia have a Stage 2 or 3 PPE [8,9]. Importantly, the incidence of empyema in children has been rising [10]: The incidence rate in children younger than four years has more than doubled in the last 20 years [11]. Despite the fact that all-cause pneumonia hospitalizations have decreased since the introduction of the seven-valent pneumococcal conjugate vaccine, hospitalizations for pneumonia complicated by infected PPE have, according to National Inpatient Sample and Census data, increased from 3.5 cases per 100,000 children in 1996–1998 to 7.0 cases per 100,000 children in 2005–2007 [12].

Multiple treatment modalities exist for PPE that range in invasiveness from antibiotics alone to thoracotomy with decortication. Four randomized controlled trials in children have examined clinical outcomes comparing video-assisted thoracoscopic surgery (VATS) and tube thoracostomy with administration of fibrinolytic agents [13–16]. Two randomized controlled trials have examined the use of tube thoracostomy with a fibrinolytic agent vs. placebo in children [17,18]. Unlike adult populations with infected PPE, death in children is rare; therefore, the primary endpoint in these studies was the number of days in the hospital after the intervention [19,20]. None of the randomized studies noted a significant difference in the primary outcome between interventions except for one single-institution study in Turkey. That study found a significant difference in post-operative length of stay between treatments, with 10 days for those with tube thoracostomy and fibrinolytic agents and seven days for VATS [14]. The authors of these studies concluded that, despite the small sample sizes, the lack of significant differences indicates that the interventions are equally effective. These findings contradict the findings of previous retrospective studies, but those likely were influenced by case selection bias [21,22].

Although the existing studies begin to address the question of the best type of intervention, they do not deal with some fundamental questions, such as the optimal timing of intervention and the relative efficacy of non-operative, antibiotic-only management. It is therefore difficult to standardize care for this group of patients. It was our hypothesis that, despite the multiple randomized trials, physicians do not agree about the optimal treatment of PPE. In order to investigate physician opinion regarding this issue, and to help inform the design and execution of a definitive intervention trial, we performed a nationwide multidisciplinary survey.

Methods

To evaluate the opinions of physicians who treat pediatric patients with PPE, we developed a survey in which questions were generated through discussion of a nationwide multidisciplinary advisory group that included pediatric surgeons,

hospitalists, infectious disease physicians, intensivists, interventional radiologists, and pulmonologists. The purpose of the advisory group was to establish the content validity of the survey questions. The study was approved by the Seattle Children’s Hospital Institutional Review Board.

Surveys were disseminated to the following professional groups: International Pediatric Endosurgery Group, American Pediatric Surgical Association, Society for Pediatric Interventional Radiology, American Thoracic Society, and the American Academy of Pediatrics Sections on Hospital Medicine and Critical Care. We attempted to include the Emerging Infections Network to sample infectious disease specialists; however, the survey was not accepted because it was believed to be too long. The survey was sent via e-mail with one follow-up e-mail as a reminder. There was a potential for overlap in the groups surveyed. For example, it is possible that someone in the International Pediatric Endosurgery Group would also be a member of the American Pediatric Surgical Association. As part of the consent process, each respondent was requested to take the survey only once no matter how many copies they received.

Each of the professional societies e-mailed to its own mailing list, which included 5,636 e-mail addresses. Informed consent was obtained for each participant prior to completion of the survey. There were previously 741 respondents. As stated in the Methods, it is likely that there was overlap between the societies, but the most conservative estimate of the response rate was 741 responses/5,636 solicitations, or 13.1%. Of those 619 respondents who included their specialty, 315 (50.9%) were surgeons, 92 (14.9%) were hospitalists, 86 (13.9%) were pulmonologists, 75 (12.1%) were intensivists, 36 (5.8%) were interventional radiologists, and 15 (2.4%) identified themselves as “other.” A majority, 430 (70.2%), of those who supplied information about their practice type spent >75% of their time in clinical practice. Nearly all who responded regarding their patient demographics and clinical practice cared primarily for pediatric patients (604; 97.3%), and nearly all had cared for pediatric patients with PPE within the past two years (587; 97.2%) (Table 1)

Descriptive statistics of the types of respondents and their opinions regarding treatment of pediatric PPE were calculated. Comparative analysis of the first-line treatment method based on the specialty of the treating physician was completed using the χ^2 , with significance set to $p < 0.05$. Analysis was completed with Stata version 12.1 (StataCorp. Stata Statistical Software, College Station, TX).

Results

Opinions regarding treatment

Twenty-six percent of the respondents (155 physicians) stated they had no standard of care among their colleagues or partners, and 79.8% (482 physicians) stated they had no written institutional guideline or policy regarding treatment of pediatric PPE. Nearly all (528; 90.3%) stated that all such patients require antibiotics, but among those who prescribe antibiotics and decide treatment duration, there was disagreement as to the appropriate duration of antibiotic administration and the timing of the transition from intravenous to oral treatment. The majority of respondents (207; 58.8%) believed that antibiotics should continue until resolution of symptoms, whereas 130 (36.9%) believed they should

TABLE 1. CHARACTERISTICS OF 741 RESPONDENTS WHO CARED FOR PEDIATRIC PATIENTS WITH PARA-PNEUMONIC EFFUSION

Characteristic	N (%) ^a
Physician specialty (619 respondents)	
Surgeon	315 (50.9)
Hospitalist	92 (14.9)
Pulmonologist	86 (13.9)
Intensivist	75 (12.1)
Interventional radiologist	36 (5.8)
Other	15 (2.4)
Percentage of clinical practice (613 respondents)	
100%	160 (26.1)
>75%–99%	270 (44.1)
50%–74%	121 (19.7)
25%–49%	38 (6.2)
0–24%	24 (3.9)
Case mix (621 respondents)	
Mostly adult (<25% children <18 years)	5 (0.8)
Mix of adult and pediatric (25%–75% children <18 years)	12 (1.9)
Mostly pediatric (>75% children <18 years)	604 (97.3)
Clinical environment (638 respondents)	
Adult/general hospital	28 (4.6)
Pediatric wing in an adult hospital	215 (35.3)
Freestanding children's hospital	372 (61.0)
Other	23 (3.7)

^aNumbers may not sum to total because of missing values.

continue for a minimum number of days. There was variability in determining the timing for transition from intravenous to oral antibiotics, with 109 (33.5%) transitioning after a specific number of days of the intravenous route, 92 (28.3%) after a minimum number of days, 58 (17.9%) for a total number of intravenous and oral antibiotic days, and 55 (16.9%) continuing intravenous antibiotics until resolution of symptoms. Of those respondents who continue antibiotics until symptom resolution, 297 (87.1%) described fever as an important symptom to resolve, 241 (70.7%) noted increased work of breathing and tachypnea as important symptoms, and 221 (64.8%) stated that they continued antibiotics until the need for supplemental oxygen was resolved (Table 2).

The respondents were split as to how often PPE required drainage, with 293 (50.6%) believing that drainage is required most or all of the time, and 287 (49.5%) believing that effusions require drainage some of the time or rarely. There were multiple absolute indications for drainage, including a mediastinal shift on chest radiography (357 respondents; 67.2%) and loculations on imaging (253 respondents; 47.7%) (Table 2). The timing of drainage usually depended on the clinical situation (236 respondents; 46.0%); however, 216 respondents (42.1%) believed that drainage should be performed as soon as possible or as soon as convenient after admission. There also was disagreement as to the optimal first-line method of drainage when this is indicated, with 176 (37.1%) and 175 (36.9%) respondents preferring a tube thoracostomy with a fibrinolytic agent and tube thoracostomy with VATS, respectively (Table 2). There were differences in preference for the first-line method of drainage depending on the specialty of the treating physician, with surgeons choosing to place a tube thoracostomy and administer a fibrinolytic

TABLE 2. OPINIONS REGARDING TREATMENT FACTORS AMONG PHYSICIANS CARING FOR PEDIATRIC PATIENTS WITH PARA-PNEUMONIC EFFUSION

Treatment factor	N (%) ^a	p
Symptom resolution ^b		n/a
Fever	297 (87.1)	
Work of breathing/tachypnea	241 (70.7)	
Supplemental oxygen	221 (64.8)	
Leukocytosis	177 (51.9)	
C reactive protein/erythrocyte sedimentation rate	121 (35.5)	
Pleuritic chest pain	114 (33.4)	
Inadequate oral intake	113 (33.1)	
Other	24 (7.0)	
Effusion on chest radiograph	10 (2.9)	
Absolute indications for drainage		n/a
Mediastinal shift on chest radiograph	357 (67.2)	
Loculations on imaging	253 (47.7)	
Elevated work of breathing	238 (45.0)	
Fever	185 (35.0)	
Size of effusion on chest radiograph	177 (33.4)	
Supplemental oxygen requirement	76 (14.3)	
Significant comorbidity	54 (10.3)	
Leukocytosis	50 (9.4)	
Elevated c reactive protein / erythrocyte sedimentation rate	38 (7.2)	
Pain medication requirement	24 (4.6)	
First-line method of drainage		n/a
Tube thoracostomy with fibrinolytics	176 (37.1)	
Tube thoracostomy with VATS	175 (36.9)	
Tube thoracostomy alone	108 (22.8)	
Thoracentesis	15 (3.2)	
Preferred first-line drainage by specialty		<0.001 ³
Surgeons		
Tube thoracostomy with fibrinolytics	108 (42.0)	
Tube thoracostomy with VATS	107 (41.6)	
Tube thoracostomy alone	36 (14.0)	
Thoracentesis	6 (2.3)	
Pulmonologists		
Tube thoracostomy with fibrinolytics	16 (24.6)	
Tube thoracostomy with VATS	25 (38.5)	
Tube thoracostomy alone	21 (32.3)	
Thoracentesis	3 (4.6)	
Intensivists		
Tube thoracostomy with fibrinolytics	14 (23.3)	
Tube thoracostomy with VATS	19 (31.7)	
Tube thoracostomy alone	24 (22.2)	
Thoracentesis	3 (5.0)	
Hospitalists		
Tube thoracostomy with fibrinolytics	22 (44.9)	
Tube thoracostomy with VATS	16 (32.7)	
Tube thoracostomy alone	11 (22.5)	
Thoracentesis	0	
Interventional radiologists		
Tube thoracostomy with fibrinolytics	11 (39.3)	
Tube thoracostomy with VATS	2 (7.1)	
Tube thoracostomy alone	13 (46.4)	
Thoracentesis	2 (7.1)	

^aAmong those respondents who believed antibiotics should be continued until symptom resolution, these were the symptoms they believed should be resolved.

^bNumbers may not sum to 100% because respondents could make multiple selections.

^cStatistical comparison using χ^2 analysis.

VATS = video-assisted thoracoscopic surgery.

agent (108 surgeons; 42.0%) or performing VATS (107 surgeons; 41.6%), whereas interventional radiologists preferred either a tube thoracostomy alone (13 radiologists; 46.4%) or a tube thoracostomy with a fibrinolytic agent (11 radiologists; 39.3%) ($p < 0.001$; Table 2). Most respondents (408; 75.3%) believed that the published evidence does not define the best intervention clearly.

Follow-up

To determine readiness for discharge, most respondents believed that patients should be off supplemental oxygen (494; 89.8%), have resolution of their increased work of breathing and tachypnea (483; 87.8%), be afebrile (433; 78.7%), have normalization of oral intake (399; 73.5%), and have no tachycardia (332; 61.1%). About half of the respondents followed pediatric PPE patients in the clinic after discharge (275; 50.6%), and of those who do see this patient population in the clinic after the hospital stay, many (198; 72.3%) obtain a chest radiograph. A minority of respondents have the patients perform spirometry (47; 17.2%) or lung volume studies (21; 7.8%). When asked to which treatment arm(s) the respondent would be willing to randomize a patient, 91.9% (340 respondents) stated antibiotics and tube thoracostomy placement with fibrinolytic agents, 90.0% (333 respondents) stated antibiotics with tube thoracostomy placement and VATS, 81.1% (300 respondents) stated antibiotics with tube thoracostomy placement, 63.8% (236 respondents) stated antibiotics with thoracentesis, 60.8% (225 respondents) stated antibiotics alone, and 11.4% (42 respondents) stated antibiotics with tube thoracostomy placement and open thoracotomy.

Discussion

In this analysis of the opinions of more than 741 physicians regarding the treatment of pediatric PPE, we noted substantial disagreement. Respondents described a lack of consensus among their partners and at an institutional level. Moreover, specific protocols for treatment modalities such as the timing and duration of antibiotics were not uniform. There was a dispute about the optimal method for drainage when this is indicated. In addition, provider subspecialty was associated with substantial differences of opinion regarding the first-line method of drainage, with 80% of surgeons choosing either tube thoracostomy plus fibrinolytic agents or VATS compared with 85% of interventional radiologists, who preferred tube thoracostomy or tube thoracostomy and fibrinolytic agents.

Although it was our suspicion on the basis of the literature that there would be significant disagreement as to the optimal treatment for pediatric PPE, it still was surprising, given that there have been four published randomized trials comparing fibrinolytic agents with VATS [13–16,23–25]. In 2006, Sonnappa et al. performed the first randomized controlled trial of pediatric PPE [16]. In their study, children younger than 16 with pleural fluid on chest radiography and ultrasound scanning, fever above 38°C for 24 h while the patient was receiving intravenous antibiotics, and respiratory distress requiring supplemental oxygen were included. The authors then compared tube thoracostomy plus urokinase infusion with VATS. They found no significant difference in length of stay after intervention, this being six days in both groups ($p = 0.3$). Secondary outcomes, including days with a tube

thoracostomy, post-intervention fever, and total days of supplemental oxygen, also were similar in the groups. Of note, their study included 60 patients, with 30 randomized to each arm; therefore, it is possible that the lack of difference was related to insufficient power.

Three years later, St. Peter et al. performed the first randomized trial of pediatric PPE treatment in the United States [15]. In their study, patients were included if they were 18 years or younger, with pleural septations or loculations on computed tomography or ultrasound scans, or leukocytosis of $>10,000$ cells/mcL on thoracentesis. The investigators randomized 18 patients to undergo tube thoracostomy with alteplase (tPA) and 18 patients to receive VATS. Similar to the study by Sonnappa et al., their primary outcome was post-intervention length of stay, and they found no difference between the groups, with seven days for each ($p = 0.96$). Secondary outcomes also did not reach statistical significance, including post-intervention fever days or days of supplemental oxygen requirement.

In 2011, Cobanoglu et al. compared 27 patients randomized to VATS with 27 patients randomized to tube thoracostomy and streptokinase infusion [14]. They included pediatric patients with confirmed Stage 2 or 3 PPE and examined overall length of stay. Unlike the previous studies, Cobanoglu et al. found that patients treated with VATS had a significantly shorter overall length of stay, seven days compared with 10 days for the streptokinase group ($p < 0.001$). The authors also noted that the time to thoracostomy tube removal was substantially shorter in the VATS group. This finding may have been biased by the study protocol, which required the tube to remain in place for a minimum of 3–5 days.

Most recently, in 2014, Marhuenda et al. completed the first multicenter randomized trial comparing 53 patients treated with VATS and 50 patients treated with tube thoracostomy and urokinase infusion [13]. The study included patients younger than 15 years with community-acquired pneumonia and a PPE requiring tube thoracostomy placement or ultrasound features of complicated effusion. Similar to the previous studies, they found no difference in post-intervention length of stay, which was nine days in the urokinase group and 10 days in the VATS group ($p = 0.45$). They did note fewer tube thoracostomy days in the VATS group (four days) compared with the urokinase group (five days) ($p < 0.001$). However, the authors found no statistically significant differences between the groups with respect to the total length of stay, post-intervention fever days, or failure rate. Of note, the four studies had variations in their treatment protocols with regard to tube thoracostomy size. Sonnappa et al. used 8–10 French percutaneous tube thoracostomies for the fibrinolytic agents group and “one or two chest drains” for the VATS group, St. Peter et al. used a 12F percutaneous tube thoracostomy for the fibrinolytic group and a 19F Blake drain for the VATS group, Cobanoglu et al. used 18–24F chest tubes in both groups, and Marhuenda et al. used 12–14F drains for the patients receiving a fibrinolytic agent and “one or two chest tubes” for those having VATS [13–16]. Despite these protocol variations, few outcome differences reached statistical significance.

In addition to the four randomized controlled trials comparing VATS and fibrinolytic therapy, there have been two published randomized trials in pediatric patients comparing fibrinolytic agents and placebo. Thompson et al. in 2002 and Singh et al. in 2004 compared urokinase and streptokinase, respectively, with a placebo infusion into the thoracostomy

tube [17,18]. Thomson et al. noted that there was a substantially shorter length of stay with the use of urokinase and saw no clinical benefit of streptokinase infusion. Similarly, a randomized study in adult patients by Maskell et al. found no improvement with the use of streptokinase rather than placebo [26].

There are many treatment options available for pediatric parapneumonic effusion that differ in their degree of invasiveness, from non-invasive (antibiotics alone) to the most invasive (thoracotomy with decortication). The method chosen thus has substantial economic implications. Cost analyses have demonstrated that VATS costs \$11,700 per patient, whereas tube thoracostomy with a fibrinolytic agent costs \$7,600 per patient [15]. On the basis of the Health Care Cost and Utilization Project estimate of 167,600 hospitalizations for pneumonia annually, and assuming 2% of these patients will have an associated infected PPE, the difference in total cost of VATS with fibrinolytic therapy would be an estimated \$13.7 million annually [2].

Despite the randomized trials that have been reported comparing treatment modalities for pediatric PPE, our data suggest that these studies do not provide conclusive evidence to guide physicians in their treatment of this patient population. All six of the published randomized trials include at least thoracostomy tube placement in all patients [13–18]. Therefore, there is little information to answer the essential question addressing the optimal timing of this intervention, and even whether it is required. It is our hypothesis that these studies have randomized patients late in the disease timeline, when the decision for intervention has already been made, and additionally reflect a bias that intervention is always required. The American Pediatric Surgical Association released a comprehensive review of the literature in 2012 that cited three factors that define the management of pediatric PPE: The size of the effusion, the presence of symptoms, and evidence of loculation on imaging [6]. On the basis of grade C evidence, Islam et al. recommended drainage for large effusions, loculated collections, and moderate-size effusions with worsening symptoms [6]. The duration of antibiotic treatment, clinical features that guide transition from intravenous to oral antibiotics, and appropriate follow-up care were not addressed. The British Thoracic Society cites level D evidence for following pediatric patients with severe pneumonia and infected PPE after discharge until their chest radiograph appears normal [5]. The ambiguity regarding these decisions is reflected in the substantial variability among respondents in opinions regarding the timing and transition of both antibiotics and invasive therapies. The current lack of conclusive data has led to substantial provider bias and variability, with statistically substantial differences in treatment approach based on the specialty of the treating physician.

Although the present report is a survey of a large, diverse group of physicians who care for pediatric patients with PPE, there are limitations. Our analysis used survey questions requiring retrospective recall and is thus subject to recall bias. Additionally, given the broad dissemination of the survey, it is likely that we sent it to physicians who do not treat pediatric PPE and thus did not respond, a likely contributor to our low response rate. An additional limitation is the lack of respondents who were infectious disease specialists, who may have had useful things to say about the duration of antibiotics and transition from intravenous to oral adminis-

tration. We attempted, but were unable, to send our survey to the Emerging Infections Network, as mentioned in the Methods section. Because we are unable to assess the attitudes and beliefs of those who were surveyed but did not respond, there is a possibility of response bias.

Despite these limitations, we believe that our results provide a provocative and vital snapshot of the variability of current treatment patterns of pediatric PPE. Our study identified substantial disagreement in treatment approaches overall and among specialties that treat pediatric patients with empyema. The published evidence does not answer basic questions about the duration of antibiotics and timing of more aggressive intervention. This paucity of data has created substantial variability in clinical practice that could be reduced with a definitive randomized trial that ensures stakeholder engagement with a disease-based rather than a physician-based framework. Now that we have identified this substantial disagreement among physicians, we hope to design and implement a multi-institutional trial in the United States that answers clinically relevant questions, such as how and when to treat pediatric patients with PPE.

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