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Therapy of 645 Children With Parapneumonic Effusion and Empyema—A German Nationwide Surveillance Study

Florian J. Segerer, MD,[1] Karin Seeger, MPH,[1] Anna Maier, MPH,[1] Christine Hagemann, MPH,[1] Christoph Schoen, MD, PhD,[2] Mark van der Linden, PhD,[3] Andrea Streng, PhD,[1] Markus A. Rose, MD, PhD, MPH,[4] and Johannes G. Liese, MD, MSc[1]*

Summary. Objective: To evaluate the initial management of pediatric parapneumonic effusion or pleural empyema (PPE/PE) with regard to length of hospital stay (LOS). Methods: Collection of pediatric PPE/PE cases using a nationwide surveillance system (ESPED) from 10/2010 to 06/2013, in all German pediatric hospitals. Inclusion of PPE/PE patients <18 years of age requiring drainage or with a PPE/PE persistence >7 days. Staging of PPE/PE based on reported pleural sonographic imaging. Comparison of LOS after diagnosis between children treated with different forms of initial invasive procedures performed ≤3 days after PPE/PE diagnosis: pleural puncture, draining catheter, intrapleural fibrinolytic therapy, surgical procedures. Results: Inclusion of 645 children (median age 5 years); median total LOS 17 days. Initial therapy was non-invasive in 282 (45%) cases and invasive in 347 (55%) cases (pleural puncture: 62 [10%], draining catheter: 153 [24%], intrapleural fibrinolytic therapy: 89 [14%], surgical procedures: 43 [7%]). LOS after diagnosis did not differ between children initially treated with different invasive procedures. Results remained unchanged when controlling for sonographic stage, preexisting diseases, and other potential confounders. Repeated use of invasive procedures was observed more often after initial non-invasive treatment or pleural puncture alone than after initial pleural drainage, intrapleural fibrinolytic therapy or surgery. Conclusions: Initial treatment with intrapleural fibrinolytic therapy or surgical procedures did not result in shorter LOS than initial pleural puncture alone. Larger prospective studies are required to investigate which children benefit significantly from more intensive forms of initial invasive treatment. **Pediatr Pulmonol. 2017;52:540–547.**

Key words: pediatric parapneumonic pleural effusion; pleural empyema; VATS; intrapleural fibrinolytic therapy.

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[1]Department of Pediatrics, University of Würzburg, Würzburg, Germany.

[2]Institute of Hygiene and Microbiology, University of Würzburg, Würzburg, Germany.

[3]Department of Medical Microbiology, National Reference Center for Streptococci, University Hospital RWTH Aachen, Aachen, Germany.

[4]Children's Hospital, Goethe University of Frankfurt, Frankfurt, Germany.

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*Correspondence to: Johannes Liese, MD, MSc, Department of Pediatrics, University of Würzburg, Josef-Schneider-Strasse 2, 97080 Wuerzburg, Germany. E-mail: liese_j@ukw.de

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INTRODUCTION

The therapeutic management of pediatric parapneumonic effusions and empyema (PPE/PE) and the impact of initial therapeutic interventions on clinical outcome are the subject of controversial discussions. A recent study from central Europe demonstrated a striking lack of consensus on the treatment of this disease.[1]

Although it has been reported that more than half of the children with PPE/PE can be managed successfully with antibiotics alone,[2] there is some evidence that early invasive draining procedures including video-assisted thoracoscopic surgery (VATS) or intrapleural fibrinolytic therapy could reduce the length of hospital stay (LOS).[3] In some studies, chemical debridement with intrapleural fibrinolytic therapy has been shown to reduce LOS compared to pleural draining catheter alone.[4] Surgical debridement with VATS has not shown any consistent evidence of superiority to intrapleural fibrinolytic therapy in studies thus far.[5–9] Recent recommendations consider antibiotic therapy alone to be a reasonable first line treatment option for complication-free small pleural effusions, and pleural drainage alone or with additional fibrinolytic therapy for many children with moderate to large PPE/PE.[10,11]

The aim of this large prospective nationwide surveillance study was to assess the current pattern of therapeutic management and to compare the effect of different initial invasive procedures on length of hospital stay of pediatric PPE/PE in Germany.

METHODS

Study Population and Case Definition

The study population included all children and adolescents <18 years of age in Germany between October 1st, 2010 and June 30th, 2013. We aimed to capture all cases of hospitalization in children <18 years of age with pneumonia-associated pleural empyema or pleural effusion requiring drainage or with persistence of PPE/PE > 7 days.

Reporting System

Prospective, active surveillance of all children hospitalized with PPE/PE for at least 1 day was carried out. Patients fulfilling the case definition were reported on a monthly basis by the Surveillance Unit for Rare Pediatric Diseases in Germany (ESPED), a nation-wide voluntary reporting system covering 476 pediatric hospitals and departments.[12] The overall response rate of all pediatric hospitals and departments in the ESPED-system is around 96%.[12] In cases where at least one patient with PPE/PE was reported, the coordinating study center (University of Wuerzburg, Germany) sent out a case report form to the reporting hospital. The physicians in charge of the patient were asked to fill out and mail back the case report form with detailed medical data.

Case Report Form

The case report form contained the following items: demographic data, preexisting chronic medical conditions, LOS, imaging procedures (including chest radiographs, ultrasound imaging, CT, and MRI), conservative and invasive PPE/PE treatment. Sonographic staging at the time of PPE/PE diagnosis was reported according to the classification of pleural effusions by Kim et al.[13]: Stage I (exudative) was defined as free-floating fluid without loculations or consolidations; Stage II (fibrinopurulent) as fluid loculated by fibrous septations; Stage III (organized) contained consolidations of >1/3 of the PPE/PE.

Outcome Parameters

The main outcome parameter in our study was LOS. Total LOS was the complete hospitalization time. With regard to different treatment modalities, LOS after the diagnosis of the PPE/PE was compared. This was defined as the time between the first radiological proof of the PPE/PE (i.e., by chest radiograph or pleural ultrasound) and the day of hospital discharge.

PPE/PE Treatment Groups

Based on the form of treatment received, the patients were classed into either a non-invasive therapy group or an invasive procedure group, which in turn was subdivided into four subgroups.

- non-invasive therapy (antibiotic treatment only)
- invasive procedures, including:
  - pleural puncture,
  - pleural draining catheter,
  - intrapleural fibrinolytic therapy via pleural catheter,
  - surgical procedures (VATS or open thoracotomy).

Grouping according to this definition was carried out with regard to treatment overall and additionally with regard to initial treatment. The initial therapeutic approach was defined as the most invasive PPE/PE treatment performed within the first 3 days after diagnosis of PPE/PE. Statistical comparisons of the main outcome parameter LOS were restricted to comparisons between the four invasive procedures subgroups with regard to initial treatment.

Statistical Analysis

Data were entered into a Microsoft® Office Access 2003 (Version 11.0) database and transferred to IBM SPSS Statistics 23 for analysis. Descriptive analysis was performed using frequencies and percentages for categorical data and median and Interquartile Range (IQR) for continuous data, respectively. Continuous variables were compared using the Mann–Whitney U-Test or Kruskal–Wallis Test and dichotomous variables using the χ^2-test.

In a survival analytic approach, LOS after diagnosis was compared between invasive procedures subgroups using the Log-rank test. In addition, a Cox Proportional Hazards model was used to adjust for the combined effect of a set of pre-defined potential confounder variables. As diagnostic plots showed signs of deviations from the proportional hazards assumption for some variables, piecewise Cox modeling was used for those variables where this approach led to a significant (at the 10% level) improvement in model fit in bivariate analyses. The rare cases of children who died in hospital were classed as censored observations and assigned the longest LOS in accordance with a "worst outcome" analysis (cf.[14] for details on the close connection between worst outcome analysis and competing risk analysis). The analyses with survival methods were performed in R for Windows 3.2.2.[15]

The pre-defined level of significance was 5%.

RESULTS

Study Population

Between 1st October 2010 and 30th June 2013, 211 pediatric hospitals/departments reported a total number of 858 children with PPE/PE. Of these, 213 cases (25%) were excluded from analysis, either due to missing case report form (n = 73; 9%), double reporting (n = 46; 5%), or non-fulfilment of inclusion criteria (n = 94; 11%). A total of 645 children with PPE/PE (75%) reported by the 211 hospitals were included in the final analysis, corresponding to an average of three PPE/PE cases per hospital (median 2, IQR 1–4, range 1–25). Half of the 645 cases analyzed in our study were reported by 45 pediatric hospitals/departments.

Main Clinical Characteristics and Risk Factors

Of the 645 children with PPE/PE, 319 (49%) were male. Patients' median age was 5 years (IQR 3–9). The median time between onset of initial symptoms and diagnosis of PPE/PE was 6 days (IQR 4–10). Sonographic staging was available for 563 of 645 (87%) cases (Stage I: 258 [40%]; Stage II: 251 [39%]; Stage III 54 [8%]).

Chronic pre-existing medical conditions were reported for 245 of the 645 children (38%). The most prevalent pre-existing chronic conditions were preterm birth (n = 70; 11%, 13 of these with a gestational age less than 32 weeks), overweight and obesity (n = 64; 10% of 645), neurologic disorders (n = 59; 9% of 645), and asthma bronchiale (n = 39; 6% of 645) or other pulmonary disorders (n = 42; 7% of 645). Children with chronic pre-existing medical conditions were significantly older than previously healthy children (6 years [IQR 3–12] vs. 4 years [IQR 3–7], $P < 0.001$). Their therapeutic management with regard to the initial invasiveness of procedures did not differ significantly from that received by previously healthy children.

Pleural fluid was recovered from 470 (73%) of 645 children. Data on the appearance of the pleural fluid was available in 362 cases; cloudy pleural fluid was reported in 258 (71%) children and clear pleural fluid in 104 children (29%). Microbiologic diagnostics detected a causative microorganism in pleural fluid in 169 cases and in pleural fluid or blood culture in 201 cases. The causative bacteria found either in pleural fluid (by culture or 16s-rDNA-PCR) or in a blood culture were the following: *Streptococcus pneumoniae* in 112 cases, *Streptococcus pyogenes* in 31, *Staphylococcus aureus* in seven, other streptococci in 13 and other staphylococci in ten cases. The identification of *S. pneumoniae* in the pleural fluid was positively associated with the use of secondary surgical interventions at a later treatment stage after an initial non-surgical therapeutic approach (OR = 2.09, $P = 0.004$).

LOS and Clinical Outcome

The median total LOS of all 645 children with PPE/PE was 17 days (IQR 13–24). Of the 645 children with PPE/PE, 375 (58%) required treatment in an intensive care unit for a median of 7 days (IQR 4–14) and 124 children (19%) needed mechanical ventilation for a median of 5 days (IQR 2–10). Seven children died (1%), including five with severe chronic pre-existing conditions.

Overall Therapeutic Interventions

Of the 645 children with PPE/PE, 142 (22%) received intravenous antibiotic therapy only throughout their course of disease (non-invasive therapy group regarding overall interventions). For these children, a median total LOS of 14 days (IQR 10–17) was reported. Their PPE/PE was classified as Stage I in 70 (49%), Stage II in 38 (27%), and Stage III in eight cases (6%). Treatment with one or more invasive procedures during the course of disease was reported for 503 (78%) children (invasive procedures group; total number of interventions n = 1091). Median total LOS for the invasive procedures group was 18 days (IQR 14–25). Their PPE/PE was classified as Stage I in 188 (37%), Stage II in 213 (42%), and Stage III in 46 cases (9%).

Initial Therapeutic Approach in PPE/PE and Effect on Outcome

The initial therapeutic approach in the first 3 days after PPE/PE diagnosis was an invasive procedure for 347 (55%) of 629 children with available data on the timing of procedures (Table 1).

The influence of the following symptoms at initial presentation on the likelihood of receiving surgical treatment as initial treatment for PPE/PE was examined in bivariate analyses: fever, sepsis, hemoglobin oxygen saturation below 92%, hemoglobin oxygen saturation below 97%, tachypnea, respiratory distress, failure to feed, chest pain. Chest pain at initial presentation was the only symptom significantly associated with the use of surgical procedures such as VATS or thoracotomy as initial treatment (OR = 2.06, $P = 0.024$).

Overall, no significant difference in median LOS after diagnosis of PPE/PE was observed between the invasive procedures subgroups defined by the initial therapeutic approach (Table 2). Analyses stratified by sonographic stage also showed no significant differences in median LOS after diagnosis between these invasive procedures subgroups (Table 3).

Kaplan–Meier analyses comparing the proportion of children discharged from hospital within t days after PPE/PE diagnosis also did not reveal significant differences between the invasive procedures subgroups (pleural puncture; pleural draining catheter; intrapleural fibrinolytic therapy; surgical procedures; log-rank test, $P = 0.567$; cf. Fig. 1). In a Cox Proportional Hazards model, the effect of the respective invasive procedures subgroup was adjusted for the combined effect of sonographic stage (I/II/III), preexisting chronic conditions (yes/no), gender, age, and time lag between initial onset of symptoms and PPE/PE diagnosis. In this fully adjusted model, the variable invasive procedures subgroup remained non-significant and all individual comparisons versus the reference category pleural puncture were also non-significant. The addition of interaction terms between invasive procedures subgroup and preexisting chronic conditions or between invasive procedures subgroup and sonographic stage did not lead to a significant improvement in model fit.

TABLE 1—Initial Therapeutic Approach and Number of Children With Secondary Interventions (Defined as Interventions More Than 3 Days After PPE/PE Diagnosis) in 629 Children With PPE/PE With Available Information on Timing of the Procedures

		Number of children with one secondary intervention	Number of children with two or more secondary interventions
Initial therapeutic approach[1] (n = 629)	n (%)	n (% of children with this initial therapy)	n (% of children with this initial therapy)
Pleural space not opened (no invasive therapy)	282 (45)	40 (14)	87 (30)
Invasive procedure	347 (55)	69 (20)	22 (6)
Pleural puncture	62 (10)	13 (21)	21 (34)
Pleural draining catheter	153 (24)	35 (23)	1 (1)
Intrapleural fibrinolytic therapy	89 (14)	16 (18)	0
Surgical procedure	43 (7)	5 (12)	0

[1]Mutually exclusive.

Treatment Failure and Secondary Interventions

Secondary interventions were defined as interventions more than 3 days after the diagnosis of the PPE/PE. One hundred thirty-nine (49%) of the 282 children who initially received only non-invasive treatment (non-invasive therapy group) had to be switched to invasive treatment at a later treatment stage. The secondary use of invasive procedures in these children was significantly associated with sonographic staging, increasing from 41% (49 of 119 children) in sonographic Stage I to 63% (66 of 104 children) in Stage II and 58% (11 of 19 children) in Stage III ($P = 0.003$).

An extensive risk factor analysis identified a subnormal hemoglobin oxygen saturation level below 97% as the only independent clinical symptom that was significantly associated with failure of non-invasive treatment alone (OR = 1.96, $P = 0.033$). The other initial clinical symptoms examined (fever, sepsis, tachypnea, respiratory distress, failure to feed, chest pain, hemoglobin oxygen saturation below 92%) were not associated with a significantly higher probability of the necessity to use a secondary, more invasive procedure.

The number of secondary interventions after the 3rd day after PPE/PE diagnosis ranged from 0 to 4 procedures and was significantly associated with the invasiveness of the initial therapy. Two or more secondary interventions were carried out in 87 (30%) of 282 children who initially received non-invasive therapy and in 21 (34%) of 62 children with initial pleural puncture, but only in one of 153 children with initial pleural draining catheter and in none of the children with initial intrapleural fibrinolytic therapy or initial surgical procedures (cf. Table 1, $P < 0.001$). There was no significant difference in the frequency of secondary interventions between children who were initially treated with pleural

TABLE 2— Length of Hospital Stay (LOS) After Diagnosis in 347 Children With PPE/PE and Initial Invasive Procedure

	Initial invasive procedure				
	Pleural puncture n = 62	Pleural draining catheter n = 153	Intrapleural fibrinolytic therapy n = 89	Surgical procedures n = 43	P-value*
LOS after diagnosis (days; median [IQR])	16 (12–29)	17 (12–24)	16 (12–23)	17 (13–26)	0.841

*P-value refers to comparison of invasive procedure subgroups, using the Kruskal–Wallis Test.

drainage, intrapleural fibrinolytic therapy, or surgical procedures.

Among children who received non-invasive therapy or non-surgical forms of invasive treatment within the first 3 days after PPE/PE diagnosis, the proportion of children receiving secondary surgical interventions (VATS or TT) in the further course of disease was associated with sonographic stage, increasing from 37 of 238 children (16%) in sonographic Stage I to 15 of 45 children (33%) in Stage III ($P = 0.003$).

DISCUSSION

This large, 3-year nationwide systematic surveillance study permitted a detailed analysis of therapeutic management and outcome of 645 children with PPE/PE. Both the long duration of hospital stay (LOS) and the fact that 58% of children with PPE/PE required treatment in an intensive care unit confirm the severity of this disease. The median LOS of 17 (IQR 13–24) days is comparable to values reported from studies in Spain (17 days)[16] and Israel (15 days).[17] However, a number of other studies have reported shorter LOS for children with PPE/PE: A study in Brazil reported a median LOS of 11 days in 102 children; however, children with very severe pneumonia and signs of bacteremia were excluded.[18] In a small prospective study with 18 patients by Kurt et al.,[19] children treated with pleural draining catheter and subsequently receiving intrapleural fibrinolytic therapy in their further course of disease had a mean LOS of 13 days compared to 6 days for children following initial VATS; the fact that the treatment was carried out in a highly specialized center may, together with the specific characteristics of the US health care system, offer a possible explanation for the considerably shorter LOS observed in that study. A similar observation was reported for a study in the U.K., with a median LOS of 7 days for 258 children hospitalized with pleural empyema between 2002 and 2009.[20]

The management of PPE/PE in our study showed wide variations ranging from antibiotic treatment only to invasive surgery by VATS/open thoracotomy. A wide variation in treatment of PPE/PE has recently also been reported from a survey carried out in Austria, France, Germany, and Switzerland.[1] This may indicate that there is a relatively high degree of uncertainness in the initial management of pleural empyema, especially in children where prospective, comparative studies are very limited.

Although 45% of patients initially received non-invasive treatment, half of these children were eventually treated with an invasive procedure, notably 63% of children with sonographic Stage II and 58% of children with sonographic Stage III. Nevertheless, therapeutic management of 22% of all children was achieved without any opening up of the pleural space, even though one third of these children had sonographically documented loculations or consolidations. Besides a decreased level of hemoglobin oxygen saturation of less than 97%, no other clinical risk factor could be identified to predict failure of treatment with antibiotics alone. In the study by Carter et al., successful therapeutic management of more than 50% of PPE/PE-patients was achieved with non-invasive treatment, even though half of these suffered

TABLE 3— Length of Hospital Stay (LOS) After Diagnosis in 347 Children With PPE/PE and Initial Invasive Procedures Stratified by Sonographic Staging[1]

	Pleural puncture	Pleural draining catheter	Intrapleural fibrinolytic therapy	Surgical procedures	*P*-value*
Sonographic stage I	n = 26	n = 69	n = 25	n = 14	
LOS (days; median [IQR])	14 (11–18)	16 (10–23)	17 (13–22)	16 (14–25)	0.365
Sonographic stage II	n = 23	n = 60	n = 43	n = 14	
LOS (days; median [IQR])	21 (13–28)	17 (13–25)	16 (12–22)	18 (13–26)	0.351
Sonographic stage IIII	n = 7	n = 7	n = 12	n = 8	
LOS (days; median [IQR])	31 (16–45)	20 (17–34)	21 (14–37)	15 (13–49)	0.824

[1]Information on sonographic stage was missing for 39 patients.
*P-values refer to comparison of invasive procedure subgroups using the Kruskal–Wallis Test.

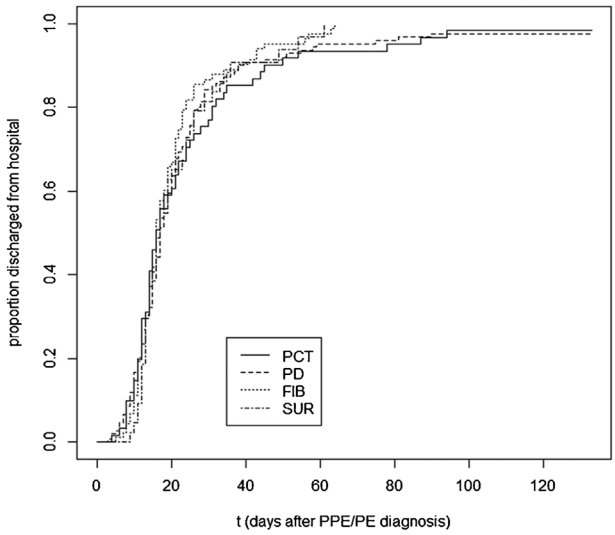

Fig. 1. Proportion of children discharged from hospital within t days after PPE/PE diagnosis, stratified by invasive procedures subgroup (with regard to initial treatment). PCT, pleural puncture; PD, pleural draining catheter; FIB, intrapleural fibrinolytic therapy via pleural catheter; SUR, surgical procedure (VATS or open thoracotomy).

from fibrinopurulent PE.[2] The treatment protocol used in that retrospective study started with i.v. antibiotics and proceeded to pleural drainage only in patients without clinical improvement after 48 hr.

In the PPE/PE cases covered in our study, a total of 1091 PPE/PE-directed invasive procedures were performed on 503 children. Children who initially received non-invasive treatment or pleural puncture alone more often required the repeated use of invasive procedures. About 30% of these children had to undergo at least two invasive procedures after the 3rd day following PPE/PE diagnosis. However, there was no significant difference in the frequency of secondary interventions between children who were initially treated with pleural drainage, intrapleural fibrinolytic therapy, or surgical procedures.

Although evidence is limited, some small prospective studies have suggested that initial fibrinolytic therapy or early VATS can lead to shorter LOS than pleural catheter alone and reduce treatment failure rates.[4,21,22] In contrast, in our large study, LOS after diagnosis did not differ significantly between the different forms of initial invasive therapy, even when the comparisons were adjusted for sonographic stage of the PPE/PE, preexisting chronic medical conditions, time-lag between initial symptoms and diagnosis of the PPE/PE, gender, and age. It is interesting to note that children with loculated PPE/PE (sonographic Stage II) did not have a shorter LOS following initial intrapleural fibrinolytic therapy compared to pleural draining catheter alone. This corresponds well to a recent study which also found no significant reduction in LOS when comparing intrapleural fibrinolytic therapy to pleural draining catheter treatment alone.[23]

The frequency of secondary surgical interventions—possibly indicating therapeutic failure after an initial pleural puncture, pleural draining catheter, or intrapleural fibrinolytic therapy—increased from 16% in children with sonographic Stage I to 33% in Stage III. However, secondary surgical procedures were not significantly less frequent after initial intrapleural fibrinolytic therapy than after initial pleural puncture or pleural draining catheter. Furthermore our results with regard to early use of VATS are confirmed by recently published data based on retrospective hospital discharge information, where VATS treatment (at any time during disease duration) was not associated with shorter LOS.[24]

Strength and Limitations of the Study

The strength of this study is the large number of pediatric PPE/PE cases covered, which, for the first time, permitted a detailed analysis of the therapeutic management of pediatric PPE/PE in Germany. This study is representative of the therapeutic options applied in PPE/PE-patients, and, to a certain extent, allowed us to carry out a comparative assessment of different therapeutic strategies. It is, however, remarkable that 58% of the children in our study required treatment in an intensive care unit and 19% needed mechanical ventilation for a median of 5 days. Possibly our inclusion criteria requiring a duration of parapneumonic effusion for at least 7 days (in children without opened pleural space) contributed to a selection of more severe cases. We emphasize that this surveillance study was not designed as a comparative treatment trial. It is remarkable, however, that, despite the considerable number of patients and extensive controlling for potential confounding factors, no clear benefits with regard to clinical outcome could be observed for initial treatment with intrapleural fibrinolytic therapy or surgical procedures.

Considering the general risk of recall or reporting bias in ESPED surveys,[12,25] it is reasonable to assume that the incidence of PPE/PE is higher than that implied by our data, which can be explained by the inclusion criteria requiring a minimum of 7 days of pleural effusions and possibly result in a selection of more severe cases. In addition more severe cases in general are more likely to be reported in the ESPED system, which primarily relies on physicians' reports. Furthermore, a center-effect cannot be ruled out, although the fact that only 211 of 476 hospitals reported PPE/PE cases in our study is put into perspective when considering the overall response rate: The overall response rate of all pediatric hospitals and departments in this ESPED-system is around 96%[12]; in fact, roughly half the pediatric hospitals/departments participating in active reporting stated that they had no

cases of PPE/PE fulfilling our inclusion criteria. On the other hand, half of the 645 cases were reported by 45 pediatric hospitals/departments including large centers, and not all reporting pediatric departments were able to offer all therapeutic options, that is, pediatric or thoracic surgery. Finally, different discharge criteria between the hospitals may potentially have influenced our results. The inclusion of a random intercept term at center level in a Cox proportional hazards model comparing invasive initial treatment groups did not, however, result in a significant center effect or lead to different conclusions regarding treatment groups.

We furthermore cannot exclude incorrect severity staging, since sonographic data was reported according to standard definitions of care at the individual hospitals and no predefined standardized protocol was used. Nevertheless, sonographic staging is a method widely available and a typical element of first line evaluations in children with PPE/PE.[5,6,26] In addition, the main findings of our study were consistent across sonographic stages.

Surgical procedures may often be used as "rescue therapy" after failure of initial treatment, and these children will typically require a long LOS. We corrected for this potential bias by restricting the statistical comparisons between procedures to initial invasive procedures performed within the first three days after PPE/PE diagnosis. An analysis using total LOS would pose potential problems because delay in recognition and logistical issues could lead to skewed results. Therefore, we used LOS after PPE/PE diagnosis in our analysis of the effect of initial therapy on LOS.

We Conclude from This Study

The initial therapeutic management of 645 children with PPE/PE varied widely from conservative therapy with antibiotics alone to invasive surgical procedures. With regard to initial invasive procedures within the first three days after diagnosis, we did not observe a shorter length of hospital stay after PPE/PE diagnosis in those children who were treated with intrapleural fibrinolytic therapy or surgical procedures, such as VATS or open thoracotomy. However, about one third of children initially treated with noninvasive therapy or pleural puncture alone, later required a secondary, more invasive intervention.

We conclude that large prospective, randomized studies comparing different invasive procedures in PPE/PE strategies are necessary to identify those children with PPE/PE who will derive significant benefit from early invasive procedures like intrapleural fibrinolytic therapy or VATS.

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