# Management of parapneumonial pleural empyema in children: a survey of the Italian Society of Infantile Videosurgery (SIVI)

Alberto Ratta,[1] Maurizio Cheli,[2] Giovanni Gaglione,[3] Andrea Volpe,[4] Gabriele Lisi,[5] Valerio Gentilino,[6] Roberto Lo Piccolo,[7] Giovanni Cobellis,[8] Fawzi Shweiki,[9] Paolo Formica,[10] Ernesto Leva,[11] Paola Midrio,[12] Daniela Codrich,[13] Michele Ubertazzi,[14] Lorenzo Nanni,[15] Vincenzo Domenichelli,[1] Maria Nobili,[16] Francesco Macchini,[17] Alfonso Papparella,[18] Enrico Ciardini,[19] Luigi Mascia,[20] Denis Cozzi,[21] Salvatore Fabio Chiarenza,[22] SIVI Executive Board[23]

[1]Pediatric Surgery Unit, Ausl della Romagna; [2]Department of Paediatric Surgery, Papa Giovanni XXIII Hospital, Bergamo; [3]Department of Pediatric Surgery, Santobono Pausilipon Children's Hospital, Napoli; [4]Pediatric Surgery Unit, Women's and Children's Health Department, University Hospital of Padua; [5]Department of Pediatric Surgery "Spirito Santo", Hospital of Pescara "G. D'Annunzio", University Chieti-Pescara; [6]Pediatric Surgery Unit, Woman and Child Department, Filippo del Ponte Hospital-ASST Sette Laghi, Varese; [7]Department of Pediatric and Neonatal Surgery, Meyer Children's Hospital, Florence; [8]Pediatric Surgery Unit, Salesi Children's Hospital, Marche Polytechnic University, Ancona; [9]Pediatric Surgery Unit, "Annunziata" Hospital, Cosenza; [10]Pediatric Surgery Unit, "S. Antonio Abate" Hospital, Trapani; [11]Pediatric Surgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; [12]Department of Pediatric Surgery, Ospedale Ca' Foncello, Treviso; [13]Department of Pediatric Surgery, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste; [14]Pediatric Surgery Unit, AOU Maggiore Della Carità, Novara; [15]Pediatric Surgery Unit, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome; [16]Pediatric Surgery Unit, University of Foggia; [17]Pediatric Surgery Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan; [18]Pediatric Surgery, Department of Paediatrics, Faculty of Medicine, Second University of Naples; [19]Pediatric Surgery Unit, S. Chiara Hospital, Trento; [20]Pediatric Surgery Unit, ARNAS "G. Brotzu", Cagliari; [21]Pediatric Surgery Unit, Sapienza University of Rome; [22]Department of Pediatric Surgery and Pediatric Minimally Invasive Surgery and New Technologies, San Bortolo Hospital, Vicenza, Italy; [23]SIVI Executive Board: Giovanni Casadio, Fabio Beretta, Cosimo Bleve, Alessio Pini Prato, Andrea Conforti, Antonio D'Alessio, Marco Gambino, Riccardo Guanà, Antonino Morabito, Simona Gerocarni Nappo, Paolo Caione, Giulia Giannotti

Correspondence: Alberto Ratta, Pediatric Surgery Unit, AUSL della Romagna, via Aleardi 12, 47924 Rimini (RN), Italy.
E-mail: alberto.ratta2@auslromagna.it

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## Abstract

The purpose of this paper was to define the specturm of management for Parapneumonial Pleural Effusion/Pleural Empyema (PE/PPE) in children in Italy. We conducted an online survey, distributed by the SIVI committee to 54 Italian pediatric surgery centers. A total of 23/54 (43%) Italian pediatric surgery centers responded. All responders (100%) required an anteroposterior Chest Radiograph (CXR) as the first imaging approach to suspect PPE, and chest Ultrasound (US) was routinely used in 96% of centers. A preoperative CT scan was routinely performed in 70% of centers. An etiological diagnosis was obtained in more than 80% of patients in 13% of centers, between 40% and 80% of cases in 61% of centers and in less than 40% of patients in 26% of centers. Empirical antimicrobial therapy with 2 antibiotics is the most commonly used therapeutic scheme (78% of centers) and targeted antibiotic therapy was used in 82% of enrolled centers. The majority of centers (57%) approached advanced-stage pleural empyema with Pleural Drain placement and Fibrinolysis (PDF); 26% of centers preferred to execute upfront Video-Assisted Thoracoscopic Debridement (VATD), and in 13% of centers, both fibrinolysis and VATD were used. In all cases (100%), urokinase was the fibrinolytic agent of choice. Broncho-Pleural Fistula (BPF) was treated conservatively with prolonged Pleural Drainage (PD) and antibiotics in 82% of centers, while the remaining 18% proposed early surgical treatment. 82% of centers proposed prolonged antimicrobial therapy for the treatment of Lung Abscess (LA), while 18% of centers preferred to execute upfront ultrasound-guided or thoracoscopic positioning of a pig-tail drain. As expected, we observed a lack of homogeneity in the treatment between the different centers: most of these have a preference for fibrinolysis over the use of primary VATD, with urokinase being the only fib-

rinolytic agent used in all centers. It would be desirable to involve as many centers as possible for the drafting of shared national guidelines in the treatment of PPE in children in Italy.

## Introduction

Community-acquired pneumonia represents the largest single cause of morbidity and mortality worldwide in children aged between 1 month and 5 years.[1] Complicated Community-Acquired Pneumonia (CCAP) is a severe illness characterized by a combination of local complications (parapneumonic effusion/empyema, necrotizing pneumonia, and lung abscess) and systemic complications (sepsis, multi-organ failure, acute respiratory distress syndrome, disseminated intravascular coagulation, and, less commonly, death).[2] PE/PPE are observed in 5-10% of all children hospitalized with pneumonia.[3] Large studies from the UK, USA, Australia, and Israel found that S. Pneumoniae is the main pathogen in children with PE, PPE, or both, and is also the most common cause of Necrotizing Pneumonia (NP).[4] The introduction of the 7-valent Pneumococcal Conjugated Vaccine (PCV7) in 2000 led to a decline in the incidence of CAP and invasive pneumococcal disease, but was associated with an increased incidence of PPE, primarily due to non-vaccine serotypes. Following the global replacement of the PCV7 with the 13-valent PCV (PCV13), which covers additional serotypes, the incidence and rate of hospitalization for PPE decreased substantially.[5] Other organisms commonly involved in the pathogenesis of CCAP are *Streptococcus pyogenes* and *Staphylococcus aureus*, whereas *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Pseudomonas aeruginosa* are less common causes.[6-7] Moreover, *S. pneumoniae*, *S. aureus*, *S. pyogenes*, *Klebsiella, P.,* and anaerobic bacteria are reported to be the most common pathogens in children with lung abscesses.[8] Previous viral illness (especially influenza) or bacterial and viral co-infection might be an important risk factor for severe CCAP in childhood. Pneumonia may result in PE, which can progress to PPE in three stages. The first stage involves an inflammatory exudate, clear in appearance, of low viscosity and sterile. Stage two results from the translocation of white blood cells in the fluid, with the deposition of fibrin in the pleural space, causing loculations of purulent fluid between the lung parenchyma and the chest wall. Stage three involves the formation of a thick membrane covering the visceral pleura, causing a rigid rind, limiting lung expansion and ventilation.[10] Management of PPE in pediatric age is still a diagnostic and therapeutic challenge due to lack of level one evidence in this population. Results from adult studies cannot be used for management decisions in children, who are normally not affected by underlying lung disease. This is in contrast to adults, where empyema carries a 20% mortality risk related to other comorbidities such as malignancy and chronic cardiovascular or respiratory diseases.[11] The British Thoracic Society (BTS) guidelines for the management of pleural infection in children recommend accurate pre-intervention ultrasonographic staging of PE, prompt insertion of an intercostal drain when indicated, and use of intrapleural fibrinolytic therapy via the intercostal drain. Some centers advocate early surgical debridement as primary treatment of advanced PPE (stage II-III) and this approach is reflected by reports in the last decade showing increased use of VATD.[2,10] Given there is no clear gold-standard management, and the diverse range of clinical presentation of these patients, significant diversity in management practices of PPE in children across Italy is expected. The aim of this study is to report the emerging data from a survey, proposed by the Italian Society of Infantile Video Surgery (SIVI), aimed at representing the different practices in the treatment of pediatric PPE between the main pediatric surgery centers in Italy.

## Materials and Methods

A 24-question anonymous online survey was designed to assess the main items in medical and surgical management of PPE in children in all 54 Italian pediatric surgery departments. The items were grouped into several main categories, including quantification of single-center clinical experience (number of cases treated in the last 5 years); diagnosis and preoperative workup; antibiotic therapy; interventions and operative techniques employed; postoperative management, treatment of NP and its complications (pneumatocele, LA, BPF), and follow-up. Ethical approval was sought from the SIVI executive committee and all Italian pediatric surgery departments were contacted electronically. The e-mail contained a link to an anonymous online survey regarding the management of PPE in children. A second round of e-mails was sent 3 months later as a reminder. Answers were collected from a series of multiple-choice options and free-text boxes. Data were analyzed using descriptive statistics and reported as frequency and percentage for each question. Free-text responses were analyzed using thematic analysis.

## Results

The survey was sent by e-mail to 54 pediatric surgery departments in Italy and responses were received by 23 (43%) institutions. The average number of cases treated in the last five years (from July 2018 to June 2023) was 19 (41-3) while the average number of patients observed by each center per year was 4 (1-10). All patients were first admitted to a pediatric emergency department or pediatric general medicine ward and then referred to the pediatric surgical team after diagnosis of CCAP.

All centers (100%) required blood tests (white cell count, total neutrophil count, C-reactive protein) as confirmation of bacterial rather than viral origin of the PPE. Blood cultures were performed routinely in 17/23 centers (74%) while samples of sputum or bronchoalveolar lavage were sent for microbiological diagnosis in 14/23 centers (61%). Routine detection of S. Pneumoniae antigen in urine was performed in 13/23 centers (57%). In all pediatric surgery centers (100%), cultures for aerobic and anaerobic organisms were performed on samples of pleural fluid collected at the beginning of pleural drainage positioning or VATD procedure. Specific polymerase chain reaction for identification of the most common bacteria and viruses was performed in 15/23 centers (65%). Overall, the set of microbiological tests performed led to an etiological diagnosis in more than 80% of patients in 3/23 centers (13%), between 40% and 80% of cases in 14/23 centers (61%) and in less than 40% of patients in 6/23 centers (26%).

All responders (100%) required anteroposterior chest radiograph (CXR) as first imaging approach to suspected complicated pneumonia (Figure1). Chest Ultrasound (US) was routinely used in 22/23 centers (96%) to confirm the presence of a pleural fluid collection, to stage a PE/PPE and to guide thoracocentesis or drain placement. Moreover the majority of enrolled centers 16/23 (70%) utilized CT scan preoperatively in order to exclude underlying pulmonary malformations, concomitant pulmonary abscess or to better understand findings obtained from CXR and US (Figure 2). No centers use chest MRI instead of CT scans to stage PE/PPE and to guide appropriate treatment.

Empirical large spectrum double antibiotic therapy with amox-

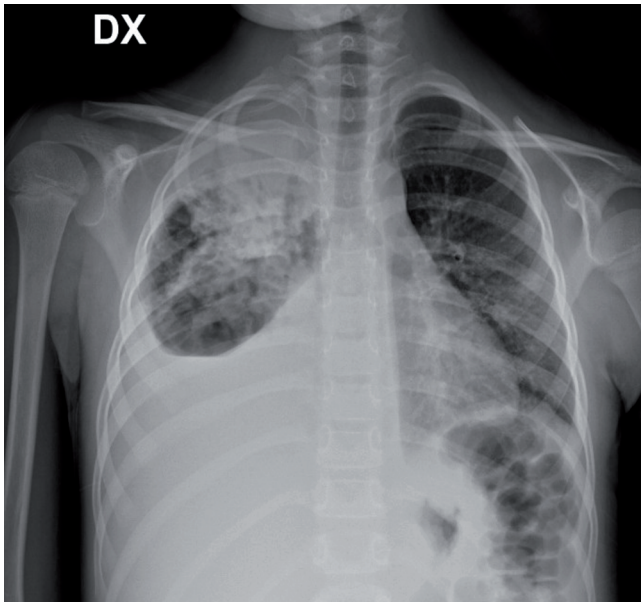


**Figure 1.** Chest XR showing a near complete opacification of the right hemitorax with atelectasia of the lower lobe. The upper lobe is partially aerated and affected by a lobar pneumoniae.

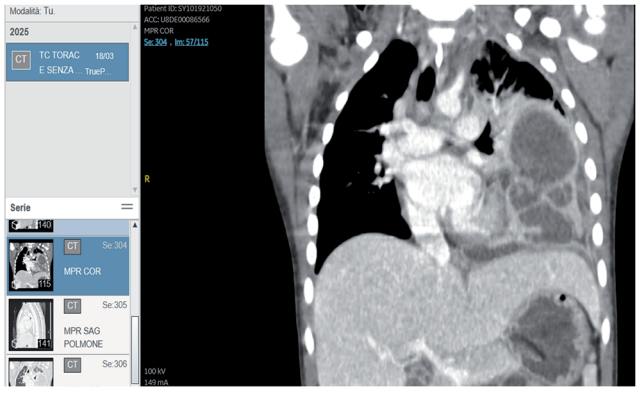


**Figure 2.** Chest CT: Left lung largely occupied by multiple fluid-filled collections. The largest, measuring 62 x 41 x 69 mm, also contains an air component and is located in the posterior half of the upper two-thirds of the left lung (abscesses).

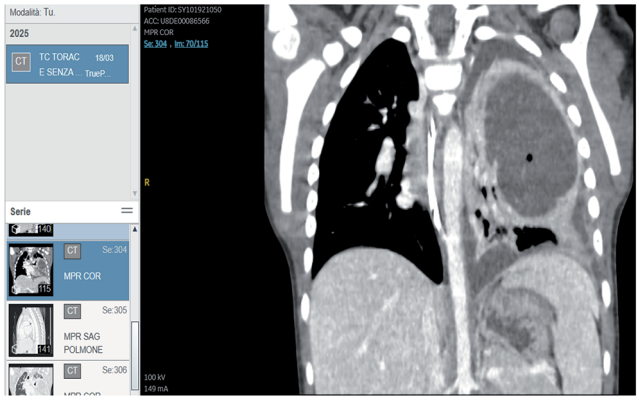


**Figure 3.** Stage II Empyema – thoracoscopic view: both parietal and visceral pleura are completely covered by a layer of fibrin.

icillin/clavulanate or second/third generation cephalosporin plus clindamycin or vancomycin is the most commonly used antibiotic regimen (18/23 centers – 78%). Single antibiotic therapy was initially adopted by only 3/23 centers (13%) and based on the use of third-generation cephalosporin (2 centers) or Linezolid (1 center). A treatment protocol consisting of three classes of antibiotics (addition of a macrolide) was routinely adopted in 2/23 centers (9%). Targeting of antibiotic therapy based on microbiological diagnosis is routinely performed in 19/23 centers (82%). The minimal duration of intravenous therapy was 7-10 days in the majority of centers (16/23 – 70%), 14 days in 4/23 centers (17%), and 21 days in 3/23 centers (13%). The overall duration of therapy was 14-28 days in most of the centers (19/23 – 82%), less than 14 days in 2/23 centers (9%) or more than 28 days in another 2/23 – 9 % of responders.

With regard to the surgical strategy, on the basis of the answers provided, the choice to provide surgical treatment is made in all centers on the basis of the stage of PPE, the clinical progress of the patient, respiratory symptoms and the efficacy of the antibiotic therapy. Stage I PPE were commonly approached with pleural drainage positioning (PD) in most of centers (18/23 – 78%). Evacuative thoracentesis with sampling of pleural fluid for microbiological identification was proposed by 3/23 centers (13%). Only 2 centers (9%) adopted a wait-and-see strategy (in paucisymptomatic patients), reserving the right to proceed to surgical treatment in the event of clinical and/or radiological decline. Stage II PPE (Figure 3) were approached with pleural drainage positioning and fibrinolysis (PDF) in most of the centers (13/23 – 57%), whereas 6/23 centers (26%) treated all fibrino-purulent empyema directly with primary Video-Assisted Thoracoscopic Debridement (VATD) (Figure 4). Finally, in some centers (4/23- 17%) the choice between PDF and thoracoscopic surgery is left to the individual surgeon who decides together with the pediatric anesthesiologist based on the patient's clinical conditions. Stage III PPE was treated in almost all centers with VATD (19/23 – 83%) while thoracotomy is still the treatment of choice in organized PPE in 4/23 centers (17%). The majority of centers that treat advanced PPE thoracoscopically (14/19 – 74%) proposed a multi-access approach (2 or 3 trocars), while 5/19 centers (26%) usually perform pleural debridement through a single port thoracoscopic access. In all centers, at the end of the thoracoscopic procedure, a pleural drain is left in place. From the thematic analysis of the open answer regarding surgical treatment, it emerged that the objective of the VATD was to remove pleural loculations, drain purulent fluid, and irrigate the thoracic cavity, but did not include an attempt to perform complete lung decortication. All centers reported sending of fluid samples

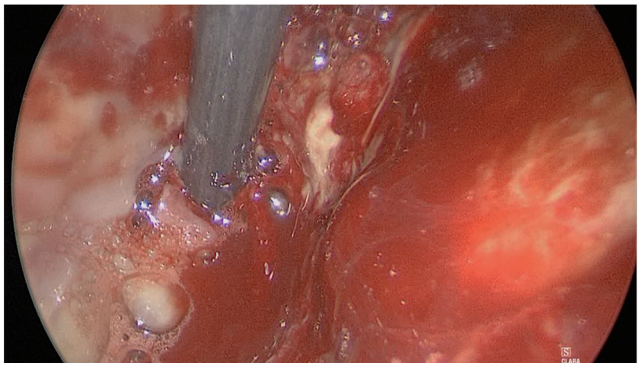

**Figure 4.** Video-assisted thoracoscopic debridement (VATD) of stage II empyema.

for microbiological assessment during the surgical procedure and performed a post-operative CXR (usually within 24h) to ensure the correct positioning of the surgical chest drain and the complete expansion of the lung. Urokinase is the fibrinolytic agent of choice in all centers (100%) and the was administered by irrigation of the pleural cavity with 10-40 ml (10 ml under 10 Kg and 40 ml over 10 kg of weight) of 1:1000 UI solution of UK twice daily for 3-5 days. No centers used other fibrinolytic agents. All centers that approached stage II PPE with PDF performed a "rescue" VATD in all cases that did not respond to the initial treatment. Almost all centers initially approached cases of NP, broncho-pleural fistula (BPF) and lung abscess (LA) with prolonged antibiotic therapy in the belief that this leads to healing without further invasive procedures. Only 1/23 centers (5%) and 3/23 centers (13%) proposed upfront surgery as the first approach in the treatment of NP and BPF, respectively. Moreover, 3/23 centers (13%) and 1/23 centers (4%) respectively approached all cases of LA with thoracoscopically assisted or US-guided drain placement. In the remaining 19 centers, thoracoscopic-assisted drainage (8/19 – 42%) and US-guided drainage (11/19 – 58%) were the treatment of choice in cases of LA that didn't heal despite prolonged antibiotic therapy. When needed, surgical correction of NP, BPF, and LA was performed in all centers with a traditional open approach.

Drain removal was performed when a clinical improvement was noted in the patient and when drain output was below 1ml/Kg/day (11/23 centers – 48%). A CXR was performed by 3/23 responders (13%) prior to drain removal, while 9/23 centers (39%) preferred to exclude any residual pleural loculations by chest US evaluation.

The majority of enrolled centers (19/23 – 70%) made use of a post-operative respiratory physiotherapy program in order to complete functional recovery. The program began during the hospital stay and was continued at home.

All patients underwent follow-up with a pediatrician or respiratory physicians for at least one year after the event. In almost all centers a radiological follow-up was scheduled with CXR performed in 16/23 centers (70%), chest US in 15/23 centers (39%), CXR and chest US in 9/23 centers (39%). Imaging follow-up was continued until complete clinical recovery and the disappearance of the pathological features at CXR and chest US. Only 4/23 centers (17%) performed a chest CT in the postoperative period but only in selected cases (suspected underlying pulmonary malformation). Respiratory functional tests were routinely executed in 14/23 centers (61%) in patients over 5-6 years old.

## Discussion

CCAP involves a spectrum of severe clinical entities that require prolonged antibiotic therapy, hospitalization, and a multidisciplinary approach. PPE can mimic uncomplicated pneumonia and should be suspected in children who persistently have a fever or remain unwell 48-72 hours after starting appropriate antibiotic therapy. Children with NP usually look ill, have a high fever, cough and experience tachypnea for several days; Hypoxia is common and PE/PPE is often detectable at physical examination or imaging. Moreover, children with NP deteriorate with progressive respiratory distress, septic shock, and acute respiratory distress syndrome. Pneumatocele and BPF are severe complications of NP, determining considerable morbidity and protracted hospitalization, and should be suspected if patients have persistent (>24h) air leak from a chest drain previously positioned or develop pneumothorax during the treatment of a severe pneumonia. Children with LA usually present with prolonged low-grade fever and cough; chest pain, dispnoea, and haemoptysis are less common. Complications of LA include pneumothorax, bronchopleural fistula, lung compression and mediastinal shift with progressive respiratory compromise.[2,12] This survey was conducted with the aim of quantifying the inter-institutional variation in the management of empyema and other complications of severe CCAP in children among pediatric surgery centers in Italy.

Antibiotic therapy is the cornerstone in the treatment of CCAP, either alone or in combination with invasive procedures. Prolonged medical treatment is also effective in treating children with NP, even when severe cavitation is present, and in most children affected by LA. Initial therapy must be effective against the most frequently involved pathogens (*S. pneumoniae*, *S. pyogenes*, *S. aureus*) and high-dose penicillin or ampicillin, amoxicillin-clavulanic acid, or second/third-generation cephalosporin (cefuroxime, cefotaxime, or cefriaxone) are often used as first-line treatment. In ICU patients, an antibiotic against methicillin-resistant *S. aureus* or anaerobic agents should be used in addition to the previously reported therapy. For children who are allergic to penicillin, clindamycin is an alternative. Antibiotics should be adjusted based on antibiograms and serology, as well as microbiology (culture for both aerobic and anaerobic organisms, and polymerase chain reaction) on biological fluids, to ensure the best possible medical treatment. The duration of intravenous antibiotic therapy is a controversial topic, and oral therapy should be started as soon as possible in the absence of respiratory distress, systemic symptoms, or elevated inflammatory markers. Typically, a course of 2-3 weeks of IV antibiotics, followed by 1-2 weeks of oral therapy, is sufficient. Similar antibiotic therapy is used for patients with NP, whereas a more prolonged therapy might be necessary for lung abscesses, which are typically slow to heal.[13-15] Data emerging from our study confirms that the approach to medical therapy of CCAP in almost all enrolled centers is coherent with local and international guidelines. Duration and type of antibiotic therapy, percentage of successful bacteriological diagnosis and related therapeutic adjustment, time to shift to oral therapy are comparable with the recommendations emerging from the international scientific literature.

CXR is always the first-line imaging technique and can show signs of parapneumonic effusion, including blunting of the costophrenic angle and a rim of fluid ascending the lateral chest wall (meniscus sign). A lateral chest radiography rarely adds anything extra, although it can sometimes be useful in differentiating pleural from intrapulmonary shadows and help raise the suspicion of a pulmonary abscess. Radiographs alone cannot differentiate an empyema from a parapneumonic effusion.[16] Ultrasonography is the primary imaging modality used to evaluate the pleural space and is more sensitive than CXR for detecting small PE, estimating the size of effusion, detecting loculations, and differentiating pleural effusion from consolidated lung changes and peripheral lung abscesses from empyema. Doppler ultrasound can detect necrotic changes of lung parenchyma early and can be used to assess the response to the treatment. The US is also useful for guiding the placement of pleural drains. In most children with PE/PPE, chest CT does not provide any additional clinically useful information compared with that gained from US, and does not predict outcomes. CT should be reserved for when there is diagnostic doubt about any concomitant malignancy or lung malformation or when appropriate treatment fails. If chest CT is deemed necessary, intravenous contrast should be given to better define the pleura and differentiate necrotizing pneumonia from lung abscess.[17] Data emerging from our survey demonstrated an extensive use of CT in order to integrate information derived from CXR and US; in fact, about 70% of interviewed centers routinely performed a preoperative

evaluation of PPE with CT. Recent studies from the literature suggest that MRI is comparable to CT for detecting various findings in children with empyema. MRI may be considered in lieu of CT, as a problem-solving tool and as a radiation-reducing endeavor in children with empyema, specifically, only when CT is required for preoperative planning and evaluation of complications.[18] None of the enrolled centers use thoracic MRI in patients with PPE.

The ideal surgical approach for PPE in children remains controversial. Guidelines from the British Thoracic Society and the American Pediatric Association recommend that non-operative intervention with fibrinolytics should be the first-line therapy in complicated PPE, as these interventions use fewer resources than operative interventions.[16,19] Complications are rarely reported with the use of fibrinolytics in uncomplicated PPE, but their use increases the risk of BPF formation in cases of NP. Regarding the choice of the fibrinolytic agent, there are no studies that have demonstrated the superiority of the most commonly used agents (urokinase, tissue plasminogen activator and Dnase) in pediatric age. Urokinase is the most commonly used fibrinolytic agent and is safe in pediatric age. Tissue plasminogen activator demonstrated similar efficacy but seems to be associated with a slightly increased risk of bleeding, while the addition of Dnase to other fibrinolytic agents had no added benefit in the treatment of PPE in children.[20,21] There is no doubt that early VATD can be an effective strategy, particularly in pediatric age, and its supporters claim that, if the child is undergoing general anesthesia for simple drain insertion, the procedure should be combined with thoracoscopic debridement. VATD debrides fibrinous material, breaking down loculations and draining pus from the pleural cavity under direct vision, enhancing healing of the affected lung, but requires specific expertise and is not widely available, especially in low and middle-income countries. In the last two decades, many different studies have suggested approaching stage II PPE with primary VATD in order to facilitate a precocious resolution of pleural infection and facilitate the healing of lung parenchyma.[22] A recent systematic review and meta-analysis found that, compared with a PDF approach, early VATD appears to be associated with a reduced need for re-intervention and a shorter post-operative hospital stay. The surgical management of organized empyema (stage III) in which a thick fibrous peel is restricting lung expansion, requires a thoracotomic or thoracoscopic decortication with complete excision of pleural rinds.[13] The results of our survey showed that the treatment of choice for paediatric PPE in Italy is pleural drain positioning followed by fibrinolytic therapy, whereas only 16% of centers treat all stage II PPE with primary VATD. On the other hand, the majority of enrolled centers (83%) treated stage III PPE with thoracoscopic debridement. Urokinase is the fibrinolytic agent used by all centers that treat advanced-stage PPE with a PDF approach.

In children with NP chest drains should be used carefully and removed early because of the risk of BPF; moreover, intrapleural fibrinolytics should be avoided because the breakdown of fibrin might result in air leaks from peripheral necrotic areas of the lung and can further facilitate BPF formation.[12] A LA coexisting with a PPE should not normally be surgically drained. The empyema should be managed in the usual way according to the single-center protocol, and the antibiotics being given for the empyema should also treat the LA effectively. In most cases, an LA doesn't require surgical treatment. US-guided drainage of the abscess through a pigtail catheter in combination with a proper antimicrobial therapy can be used for the treatment of LA resistant to antibiotics. Thoracoscopic drainage might be an effective alternative treatment and can be done together with pleural debridement in case of concomitant PPE.[8,10] Pneumatocele usually regresses over weeks to months when the infection is definitively controlled by antibiotic therapy; only a small number of giant cysts may become tense, infected or may open in the pleural cavity, requiring a segmental or lobar resection.[24] Different approaches have been advocated for a BPF associated with PPE. Most fistulae are peripheral and frequently resolve with continued chest drainage and antibiotics. Particularly severe BPF resistant to conservative treatment might require bronchoscopic fistula sealing with blood patch, fibrin glue patch, or endobronchial occlusion with one-way bronchial valves.[25] Major surgery should be limited to those few patients with complicated pneumonia who are unresponsive to medical treatment and interventional procedures. Resection of affected lung, partial pleural decortication followed by pleurodesis and/or muscle flap positioning have to be considered in chronic BPF.[10]

The timing of elective chest tube removal depends on several different factors but is essentially a clinical decision. Most clinicians take into account the amount of fluid drained, the child's temperature and general conditions as well as the value of inflammatory markers. There is no evidence to guide the decision and no substitute for clinical experience, but it is usually not necessary to wait for pleural fluid output to reach zero. US evidence to confirm the absence of a significant amount of pleural fluid may be useful. Permanently blocked drains should be removed and replaced if necessary.[10] Most of the enrolled centers decide to remove chest drains based only clinical criteria; only 13% and 39% of centers, respectively, performed a CXR or a US before removal.

Despite the lack of clear recommendations about the efficacy of respiratory physiotherapy in patients treated for PPE, 70% of the centers provided post-operative respiratory physiotherapy. Children should be followed up after discharge until they have fully recovered and their chest radiography has returned to normal. CXR will inevitably be abnormal at discharge and should be done at 4-6 weeks. The timing of further follow-up has to be scheduled based on clinical evolution and radiographic findings. In most cases CXR will return to normal by 3-6 months. The majority of affected children are previously healthy individuals and a prolonged follow-up is not necessary. Tests of immune function and a sweat test should be reserved for the small number of patients with a history of significant multiple bacterial infections. Spirometry abnormalities are common in the first few months after discharge but tend to normalize with time. Clinically important phenomena persist in the short-term after children are discharged from hospital with PPE, but 1-year outcomes are excellent.[10,26] In almost all centers included in this study an imaging follow-up was scheduled and prolonged until complete clinical recovery and the disappearance of the pathological features at CXR and chest US. Only 17% of centers performed a chest CT in the postoperative period but only in selected cases (suspected underlying pulmonary malformation). Respiratory functional tests were routinely performed by about 60% of centers in patients aged 5-6 years and over.

## Conclusions

We reported the results emerging from the first survey of Italian pediatric surgery centers dedicated to the management of parapneumonic pleural empyema in children. As expected, we observed a lack of homogeneity in the treatment between the different centers, most approaching surgical treatment of empyema with chest drain positioning and fibrinolysis, despite VATD representing a safe and viable option. Therapeutic strategies should be based on local experience, although there is moderate evidence suggesting VATD may result in lower re-intervention rates and decreased hospital length of stay. A multidisciplinary approach

with radiologists, physicians, and surgeons is essential in managing PE/PPE.

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