REVIEW

Clinical practice: treatment of childhood empyema

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Abstract

Introduction The incidence of empyema in children is increasing. Adequate knowledge of treatment modalities is therefore essential for every pediatrician. At the university hospital of Leuven, the incidence per 100,000 admissions increased from 40 in 1993 to 120 in 2005. The treatment of choice, however, is still a matter of debate. This is mainly due to the scarcity of prospective randomized trials in children but is further complicated by the absence of uniform terminology. This review starts with clarifying definitions of empyema and complicated versus noncomplicated parapneumonic effusion. The place of different imaging techniques—ultrasound, chest X-ray, computerized tomography and magnetic resonance imaging—is illustrated. All treatment steps are evaluated starting with antibiotic choices, duration of i.v. and oral antibiotics, pleural fluid analysis, indications for chest drain placement, and fibrinolysis. As to the surgical interventions, there is at present insufficient evidence that early surgery is superior to noninvasive medical treatment. Therefore, video-assisted thoracoscopy cannot be advised as general first-line therapy. *Conclusion* Since the pathogenicity of empyema is a dynamic process, therapeutic strategy must be decided based on empyema stage and clinical experience. Each referral center should agree on a diagnostic and therapeutic flowchart based on current evidence and local expertise. The flow chart outlined for our center is presented.

Abbreviations

PE	parapneumonic effusion
CPE	complicated parapneumonic effusion
UPE	uncomplicated parapneumonic effusion
VATS	video-assisted thoracoscopic surgery
BTS	British Thoracic Society

Introduction

Despite the plethora of reviews and expert opinions on this topic, there is no consensus on the most appropriate treatment of empyema. The main reason is the low number of prospective randomized controlled studies comparing different treatment modalities in pediatric patients. It must be stressed that childhood empyema differs from adult empyema in terms of causative pathogens, patient characteristics, and outcome.

Epidemiology

Empyema or "pus in the thoracic cage" as a complication of bacterial pneumonia is a disease feared in older days for its high mortality. Despite effective antibiotics and childhood vaccination programmes, parapneumonic effusions (PE) are not uncommon. In a retrospective study, Byington et al. found, among 540 children admitted to hospital with community-acquired bacterial pneumonia, 153 (28%) with PE [6]. For pneumococcal PE, an incidence of 3.3 per

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100,000 children has been documented in the USA in the years 1988–1994 [14]. Since the 1990s, a rise in hospitalization for this complication has been reported in the USA [6, 29, 32] as well as in the UK [22, 26]. In all reports, *Streptococcus pneumoniae* remains the most important pathogen. The role of the conjugated pneumococcal vaccine in the increasing prevalence of PE and the contribution of specific serotypes has been questioned [4, 5, 29]. In our unit at the university hospital of Leuven, the PE incidence per 100,000 admissions increased from 40 in 1993 to 120 in 2005. This was before the generalized introduction of the conjugated pneumococcal vaccination in Belgium [37]. The above-mentioned figures indicate that pediatricians will encounter this condition in their practice. Therefore, up to date knowledge on treatment modalities is of great importance.

Definitions

The absence of evidence-based data on empyema treatment may not be the only reason for the current treatment controversies. Throughout the literature, definitions used in this field differ substantially, hampering the comparison of individual studies and translating the findings into clinical practice.

The word "empyema" is Greek. It comes from "pyon," meaning pus and refers to the accumulation of pus in a cavity of the body. When used without further specification, it refers to "thoracic empyema." In most studies, empyema is used when punctured pleural fluid resembles pus. This remains a subjective impression and does not take into account the continuum of PE development. Occasionally, a positive culture or gram stain with macroscopically nonpurulent pleural tap is also called empyema [36].

Parapneumonic effusions are pleural fluid collections developing secondary to an adjacent bacterial infiltrate. According to the criteria of RW Light [18], parapneumonic effusions are exudates (as opposed to transudates) if at least one of the following criteria is fulfilled: (1) pleural fluid lactate dehydrogenase (LDH)/plasma LDH>0.6 of pleural >200 IU/l, (2) pleural fluid protein/plasma protein >0.5, (3) with a glucose levels <60 mg/dl. The development of PE is a continuum from clear fluid with low numbers of white blood cells to overt pus. Somewhat arbitrarily, this continuum is subdivided into three stages [13]:

1. "Exudative stage" with low white blood cell counts
2. "Fibrinopurulent stage" with abundant white blood cells, fibrin deposition, and possible formation of loculi
3. "Organizational stage" characterized by fibroblast infiltration and formation of fibrous pleural peel, the presence of which may hinder lung re-expansion

How do the terms "complicated" and "noncomplicated PE" fit into these three categories? Uncomplicated PE usually fits in with stage 1, while for stages 2 and 3, the term complicated would be appropriate. However, some authors define PE as complicated if not resolving under conservative treatment. The latter distinction, however, is of little use for guiding treatment since it is based on a *post factum* classification.

Staging empyema

Pleural fluid analysis

In clinical practice, PE staging is not straightforward. Pleural fluid analysis has long been used to classify pleural effusions based on the following characteristics: high numbers of polymorphonuclear leukocytes, LDH> 1,000 IU/l, glucose <30 mg/dl, and pH<7.2 [13]. These criteria were developed for adult patients to distinguish between infectious PE and noninfectious PE. Yet, their application to pediatric effusions has not been formally validated. Although in adults no clear correlation was found between pleural fluid characteristics and outcome [23], most guidelines include these criteria for PE treatment in adults. In a retrospective pediatric series, pleural fluid pH<7.27 correlated with fibrin septation and need for interventional therapy [7]. In a second study in children, a pH<7.2 on pleural tap, especially if combined with low pleural glucose, was associated with a high rate of (re-) intervention [19]. Care has to be taken when measuring pleural pH since residual air or lidocain in the syringe and/ or analysis delay significantly alter pH values [24].

Imaging

Ultrasound imaging gives some idea on staging but does not provide a high level of accuracy. It does estimate the size of the effusion and reveals the presence of loculi and/or pleural thickening [17]. (Fig. 1). Ultrasound staging correlates with pleural fluid markers like pH [7] and can be used to guide chest tube insertions (Table 1) [15].

Chest computerized tomography (CT) should not be performed routinely in the context of PE since it is even less suitable for staging. It gives, however, detailed information on anatomy and location of the infectious process (pleural *versus* pneumonic). It can help to guide chest drain placement or to prepare for surgery as discussed below.

Pericardial effusion may be an incidental finding on imaging. A surprisingly high incidence of pericardial effusion concomitant with PE has been reported in the very sick child [27]. However, specific treatment is rarely needed.
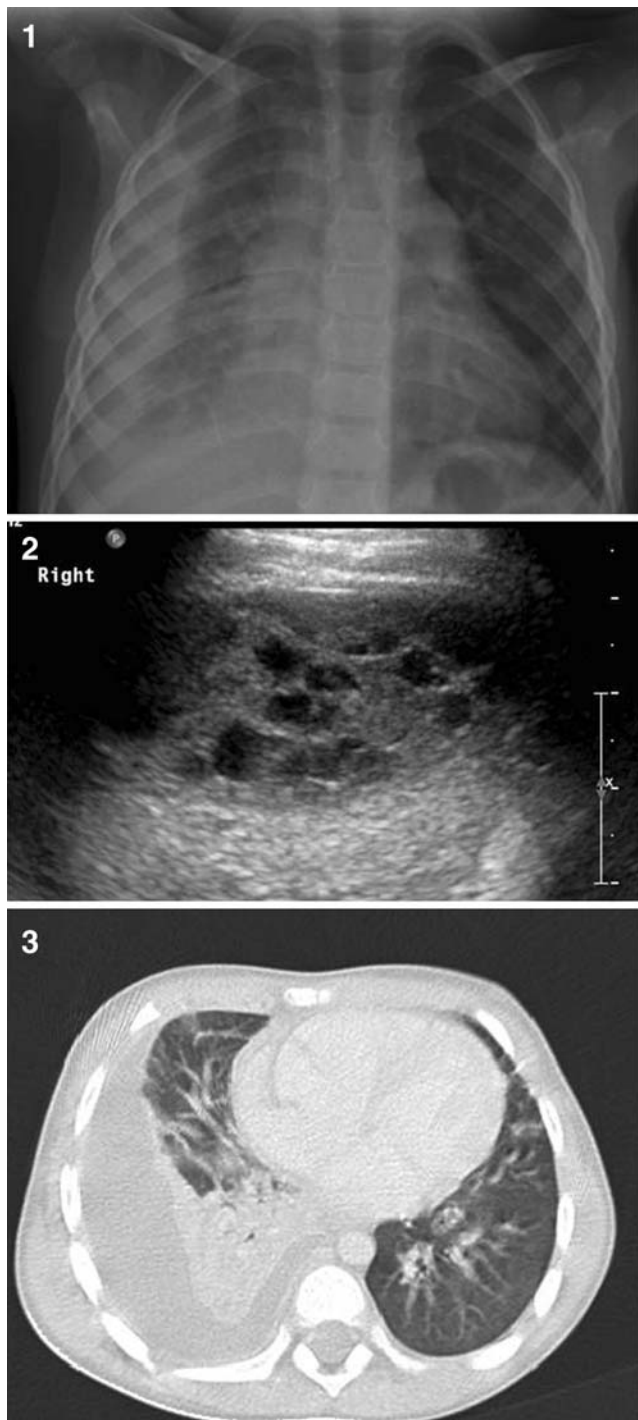
Fig. 1 Imaging for PE. The chest X-ray shows a pneumonia in the left lower lobe with ipsilateral pleural effusion. US clearly shows loculations. CT chest clearly demarcates pneumonia versus pleural effusion but cannot demonstrate loculations

Magnetic resonance imaging (MRI) can detect loculi and differentiates between inflammatory and noninflammatory changes if contrast enhancement is used [21]. At present, the restricted availability of MRI together with logistic problems limits it use in acutely sick children.

Treatment options

The aim of empyema treatment is to sterilize pleural fluid and restore normal lung function. The importance of secondary end points such as short hospital stay, low cost, and reduced invasiveness are subject of debate. There are several options in the treatment of PE: antibiotics, chest drainage, fibrinolysis, and surgical debridement. With the current arsenal, the outcome of PE is good: in Western countries, the mortality is low provided there is no associated disease such as immunodeficiency, neurological disorders, and others.

Antibiotics

There is no doubt that the first step is antibiotic therapy. Experts agree that children with PE should be hospitalized and treated with antibiotics intravenously [2]. Since in most cases the etiologic microorganism remains unknown, many clinicians are tempted to use the most "exotic" antibiotic especially when fever does not resolve. Epidemiological studies point convincingly towards *S. pneumoniae* as the most frequent organism with an increasing incidence of serotype 1 [10]. In a prospective study by Obando et al., 79% of the 208 children with PE had a positive culture for *S. pneumoniae*, and half of them were identified as serotype 1 [20]. In a Spanish study, pneumococcal DNA was detected by polymerase chain reaction in about 87% of 88 pediatric patients with culture-negative empyema fluid [33]. The increase in pneumococcal PE does not appear to be related to concurrent penicillin resistance [6]. In many countries, *Haemophilus influenzae* type b is no longer the second most important germ to cause PE in children since most children have been vaccinated against this bacterium. Therefore, *Staphylococcus aureus* is the second bacterium to be considered. Although rare, the possibility of *Mycobacterium tuberculosis* should always be kept in mind in affluent populations. Anyway, to start with, good pneumococcal coverage is of utmost importance in the antibiotic choice and dosage [2]. Knowledge of the local pneumococcal resistance pattern is hereby essential. Anti-staphylococcal antibiotics are indicated in young children, in case of necrotizing pneumonia or progressive disease. Broad-spectrum antimicrobials may be indicated for hospital-acquired disease, PE following aspiration, surgery

Table 1 Ultrasound to stage pleural effusions [15]

Stage 1	Anechoic fluid
Stage 2	Echoic fluid without septation
Stage 3	Fibrinous septation of pleural fluid
Stage 4	Septations with solid appearing components comprising >1/3 of effusion

trauma, and for patients with underlying immuno-deficiency. If the causative bacterium and the antibiotic susceptibility are known, antibiotic spectrum should be as narrow as possible.

Less straightforward than the antibiotic choice is the duration of i.v. and oral therapy. The British Thoracic Society (BTS) guidelines are vague, suggesting oral anti-biotics for 1 to 4 weeks after discharge and even longer in case of residual disease. It seems careful to continue i.v. antibiotics for at least 5–7 days after resolution of fever which in practice will be some 10 to 14 days in total. In our retrospective study on 68 pediatric patients, median hospital stay (with i.v. antibiotics) was 22 days, the days before referral not being included [37]. Our data were obtained before fibrinolysis was introduced on a systematic basis. A French group reported very similar duration of hospitaliza-tion [3]. Some series report a much shorter stay in hospital when only days after the intervention (drain or surgery) were counted [34].

To drain or not to drain

Treatment dilemmas arise when pleural fluid volume increases and the child remains febrile despite adequate antibiotic treatment. The different modalities are (1) thoracocentesis, (2) chest drain with or without (3) fibrinolysis, and (4) surgery.

In case PE exceeds 1 cm on ultrasound, a tap is indicated. Pleural fluid analysis confirms the diagnosis, excludes unusual other causes of PE, helps with staging, and allows for bacterial identification. Some patients only need a single diagnostic evacuating puncture. Few studies compared repeated puncture with drain insertion. Both procedures were found to be comparable in nonrandomized studies. Yet, some authors consider repeated puncture more traumatic for the child [2]. Low pleural pH and glucose may support the need for drain insertion [19].

For small effusions, intervention with chest drain placement or surgery does not seem to alter outcome, although only retrospective data are available. In patients with PE without mediastinal shift or respiratory distress, duration of fever, antibiotic therapy, and hospital stay were not different in conservative treated patients compared to patients with a surgically inserted drain [11]. Similarly, patients with low degree of fibrous organization of PE on ultrasound had similar length of hospital stay whether treated with conservative or operative measures [25]. In case of enlarging effusion or respiratory compromise with or without persistent fever, antibiotics alone do not suffice. Only three retrospective studies with a total of 61 patients report on the outcome of chest drain only: mean hospital stay was between 14 and 24 days, and treatment failure was around 10% [16, 28, 30].

Since PE stages 2 and 3 are characterized by fibrin deposition and peel formation, fibrinolysis has been advocated for "enzymatic debridement." In one study, 60 children with PE were prospectively randomized for treatment with thoracic drainage with or without urokinase. The dose of urokinase used is 40,000 units in 40 ml saline for children aged 1 year and above; for children under age 1, 10,000 units in 10 ml is used. This dose is given twice daily for 3 days. [34]. There was a statistically significant difference in duration of hospital stay after intervention: 7.4 days for drain plus urokinase *versus* 9.5 days for drain only (*p*=0.027; CI 1.16–1.40). A major weakness of this otherwise important study is the loose definition of empyema (not based on pleural fluid analysis) and lack of any attempt for staging. Uncommon side effects of fibrino-lysis are bleeding and allergic reaction or anaphylaxis; the latter does not occur with urokinase which is a natural product.

While a large bore surgical drain is often believed to be more efficient, a post hoc analysis of a study comparing video-assisted thoracoscopic surgery (VATS) and urokinase (see below) was in favor of small percutaneous drains by the Seldinger technique [31]. We changed our policy and now use this latter technique. It saves general anesthesia and reduces pain while encourag-ing the child's mobility.

When to call the surgeon in?

In case of treatment failure with chest drainage with or without fibrinolysis, surgical intervention for pus removal and pleural peeling becomes unavoidable. One single prospective randomized study comparing thoracotomy with debridement (in 35 patients) with "simple" chest tube placement (in 31 patients) favors the former technique for shorter hospital stay and earlier resolution of fever [30].

Over the past years, new techniques were developed such as video-assisted thoracoscopy which is less traumatic. Since then, early use of VATS has been advocated by many. Yet, all studies on the outcome of VATS are retrospective in nature. Although two meta-analyses conclude that primary surgery has the advantage of shorter hospital stay and shorter duration of antibiotic treatment [1, 12], it should be kept in mind that retrospective studies always carry the risk of bias especially concerning differences in patients' charac-teristics at baseline. The only prospective randomized trial comparing VATS with drain plus fibrinolysis could not show any difference in terms of hospital stay, days with drain, or treatment failure [31]. This study again has the problem of defining empyema. Although ultrasound staging was per-formed, no pleural fluid data were used for inclusion. In addition, the two groups of patients were heterogeneous in terms of days before admission or intervention, some

patients being ill for more than a month before inclusion. All this complicates the translation into daily practice.

In the UK, there is no consensus on the surgical dilemma [2]. There is no doubt that early surgery can be an effective strategy for certain patients, but it is costly and invasive. As long as superiority of early VATS over drainage plus fibrinolysis has not been proven in children, it cannot be advised as first choice early treatment for all. The most important element in deciding whether or not to go for surgery is the local surgical experience and availability.

Sense and nonsense of supportive therapy

Treatment dilemmas should not overlook some basics: adequate pain relief and judicious fluid and caloric intake are of utmost importance. Moreover, beware of the syndrome of inappropriate antidiuretic hormone secretion.

In many centers, children admitted with PE are given chest physiotherapy. However, since PE is about parenchymal and pleural disease, there is no indication for airway clearance. Physiotherapists should be reserved for patients with potential benefit of this treatment [9]. Along the same

lines, cocktails of nebulized drugs including mucolytics are not only useless but trouble for the patient and cost for the hospital. Also, bronchoscopy is not indicated since PE is not an endobronchial disease.

Guidelines

In spite of limited evidence, the BTS published guidelines on the management of empyema in children [2]. The first advice is a diagnostic tap whenever possible. It is a logical approach, but in practice, it is often omitted because of lack of expertise. In case of volume effect and persisting fever, further steps are warranted. The choice for early surgical versus medical treatment is left at the discretion of the treating physician, although preference for the medical approach is clearly supported. Fibrinolysis is only advised in case of thick pus or loculi.

An interesting point of discussion in clinical decision making at this stage is the place of chest CT. Cost as well as radiation force us to cut down on this radiological tool. Yet one should acknowledge that CT provides interesting

EMPYEMA = if one or more of the following
pH < 7,2
LDH > 1000 iU/l
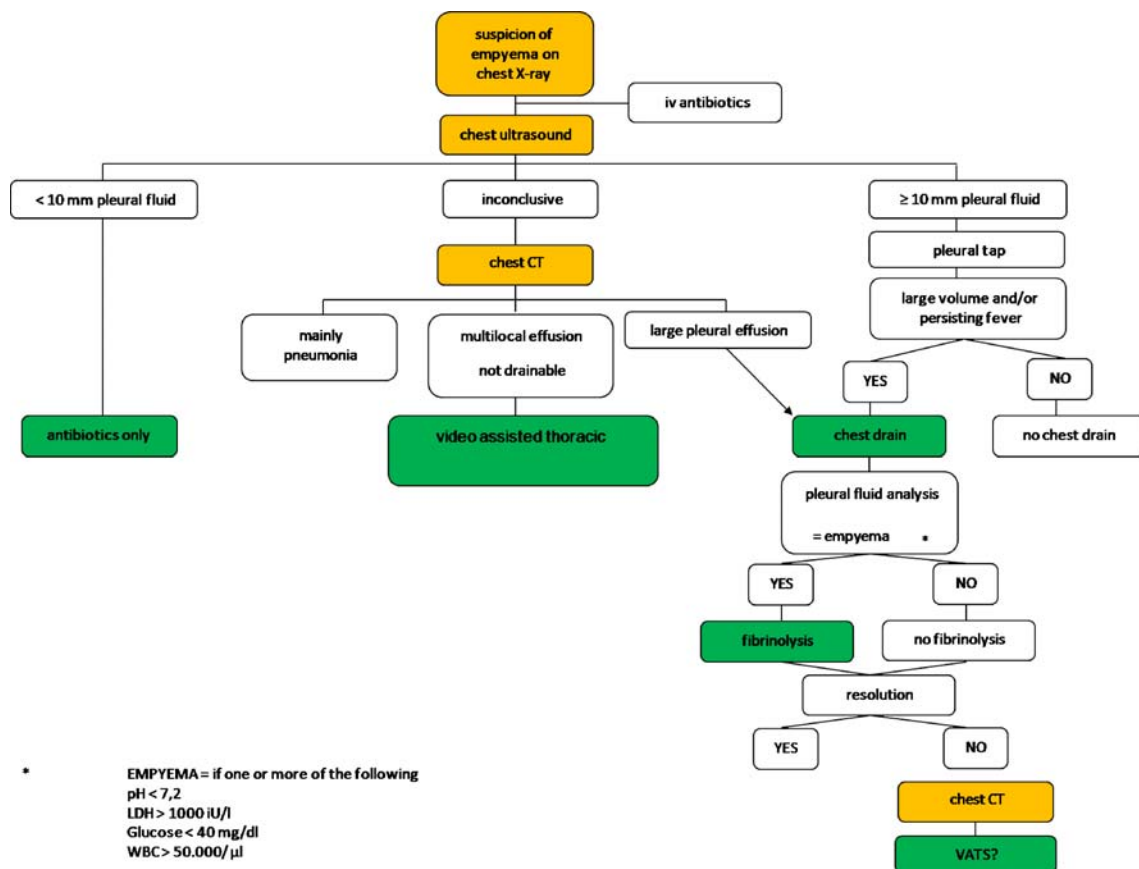Glucose < 40 mg/dl
WBC > 50.000/µl

Fig. 2 Flowchart for treatment of childhood empyema based on current literature and local medical and surgical expertise

additional information that is operator independent and answers the following questions: (1) Where ends the pneumonia and where begins the pleural collection? (2) Is there necrotizing pneumonia with abscess formation or pneumatoceles? (3) Are the airways open? (4) Are there clues toward underlying lung disease such as congenital pulmonary airway malformation?

In most PE patients, this information is redundant since a very experienced pediatric radiologist may deduce most of this information from standard chest X-ray and ultrasound. Yet when surgery is indicated, CT information may be vital in order to prevent surprises at the time of intervention. In the study comparing VATS and urokinase [31], neither ultrasonography (US) nor CT scoring on admission correlated with length of hospital stay. Although the authors conclude that the additional information provided by CT did not change clinical decision making, we feel that the study setup does not allow for such a firm conclusion. In line with the authors and with the BTS guidelines, we do not advocate routine use of CT in guiding PE treatment. PE still remains a severe disease, and in selected children, CT can help to make difficult decisions.

A flowchart

In order to streamline clinical practice in our unit, we designed a flowchart for the treatment of PE (Fig. 2). It is based on existing literature data as well as on personal clinical experience of pediatric pulmonologists and thoracic surgeons. Practical and financial issues are taken into account.

What is needed to achieve a better consensus on empyema treatment?

First of all, clear definitions are needed. Only when the terms empyema, UPE, and CPE are uniform, selection of patients for trials and translating trial data into clinical practice become straightforward.

Additionally, easy to use staging parameters correlating with outcome would help in guiding therapy. IL-8 and TNF-α levels in pleural fluid have been evaluated as markers for staging PE [8, 35, 36], and IL-8 may be promising for discriminating between CPEs and UPEs in children. In another report, inflammatory cytokines (Il-1 β and plasminogen activator inhibitors) as well as pH$<$7.3 correlated with the need for intervention [37]. Finally, more prospective randomized comparative data on VATS versus drain plus fibrinolysis are needed.

Conclusion

There is no "one size fits all" treatment for PE

The pathogenicity of empyema is a dynamic process: it is not feasible to manage all stages of PE with a single therapeutic strategy. Management must be decided on a case-by-case basis and requires clinical experience. Since outcome is usually good and evidence comparing treatment regimens are scarce, there is not one single optimal treatment. Key steps to success are expertise and a clear management plan adapted to the stage of the disease. Early referral to a pediatric center with expertise is important not to miss a critical time window and should be done before the organizing stage has set in. Key steps in treatment are diagnostic thoracocentesis, preference for small percutaneous drain, and considering fibrinolysis in the early empyema stage. Each referral center should outline a diagnostic and therapeutic flowchart, based on current evidence, local expertise, availabilities, and financial resources. The jury for early VATS is still out, but if surgery is needed, VATS by a thoracic surgeon with expertise in treating children is the best option.

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