

Management of Empyema in Children

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Summary. The incidence of empyema complicating community-acquired pneumonia is increasing and causes significant childhood morbidity. Pneumococcal infection remains the most common isolated cause in developed countries, with *Staphylococcus aureus* the predominant pathogen in the developing world. Newer molecular techniques utilizing the polymerase chain reaction have led to an increase in identification of causative bacteria, previously not isolated by conventional culture techniques. This remains an important epidemiological tool, and may help in guiding correct antibiotic use in the future. There are many treatment options, however, and the care a child currently receives is dependent on local practice, which is largely determined by availability of medical personnel and their preferences. Although there are many reported case series comparing treatment options, only two randomized controlled studies exist to guide treatment in children. There is an urgent need for this to be addressed, particularly with the introduction of relatively new surgical techniques such as video-assisted thoracoscopic surgery. **Pediatr Pulmonol.** 2005; 40:148–156. © 2005 Wiley-Liss, Inc.

Key words: empyema; fibrinolytics; video-assisted thoracoscopic surgery; children.

INTRODUCTION

The worldwide incidence of empyema is increasing,^{1–4} but it is clear that most children recover irrespective of the treatment they receive. However, the recent publication of guidelines on the management of pleural infection in children by the British Thoracic Society⁵ (BTS; www.brit-thoracic.org.uk) highlights the lack of grade A evidence available to inform best management.⁶ The treatment children currently receive is based on previous physician experience and local biases, as well as availability of trained personnel and equipment. The BTS guidelines comprehensively reviewed the evidence available for guiding the management of empyema, and for fear of reinventing the wheel, the reader is encouraged to read these guidelines in conjunction with this paper. This State of the Art will discuss briefly the issues with regard to the diagnosis of parapneumonic effusions and empyema infection, and then discuss in greater detail the management options available.

EPIDEMIOLOGY

It is estimated that 0.6% of childhood pneumonias progress to empyema, affecting 3.3 per 100,000 children.³ Many studies suggested that the prevalence of empyema complicating childhood pneumonia is increasing in both the US and UK, although this is not universally reported.^{1–4}

A recent survey from Texas suggested that the prevalence has decreased, perhaps attributable to the local introduction of a polyvalent pneumococcal vaccine.⁷ The reason for the generally reported increase in prevalence is unknown. It may relate to a reduction in primary-care antibiotic-prescribing to “chesty children,” most of whom have viral colds but some of whom have early bacterial pneumonia, thus missing an opportunity for early treatment.⁶ The disease has significant morbidity in childhood but rarely causes death, in comparison to adult empyema, which has an estimated mortality of 20%.⁸ Therefore, data from adult studies should not be

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extrapolated to children, who are almost always healthy prior to the onset of pneumonia and empyema.

PATHOPHYSIOLOGY

Normally, the pleural space contains 0.3 ml of pleural fluid per kilogram body weight. The pleural circulation is finely balanced by secretion and absorption of pleural fluid by lymphatic drainage. When this balance is disturbed by infection, pleural fluid will accumulate. Infection results in pleural inflammation with increased vascular permeability, and an influx of bacteria and inflammatory cells such as neutrophils. This inflammatory cascade is further increased by cytokine release from mesothelial cells.⁹ Activation of the coagulation cascade leads to decreased fibrinolysis and the deposition of fibrin, which cause the classic loculations and peel formation seen in later stages.

DEFINING AND STAGING EMPYEMA

Parapneumonic effusions are pleural collections in association with underlying pneumonia. The term empyema is attributed to this fluid if it contains pus. The American Thoracic Society further divided the empyema process into three stages: 1) exudative, in which the pleural fluid is low in cellular content; 2) fibrinopurulent, in which frank pus is present and there is an increase in white cells, and fibrin formation begins to cover the pleura with the formation of loculations; and 3) organizing, in which there is thick peel formation by fibroblasts and the pleural space is characterized by a “very thick exudate with heavy sediment.”¹⁰ Hamm and Light added another stage that precedes the exudative stage, which they termed the “pleuritis sicca stage.”¹¹ In this stage, there is inflammation of the pleura, manifested as chest pain and a pleural rub, which may not necessarily proceed to the exudative stage. In an attempt to help guide management, Hamm and Light ascribed pH and lactate dehydrogenase (LDH) levels to help define each stage.¹¹ In the exudative stage, the pH is normal and LDH is less than 1,000 IU. In the fibrinopurulent stage, the pH is less than 7.2 and LDH is greater than 1,000 IU. However, it must be noted that these values are applicable to adult patients and have not been properly validated in the pediatric population, although some pediatric papers suggested that pH may be a useful prognostic marker.^{12,13} The BTS guidelines felt there was no place for routine biochemical analysis of pleural fluid in guiding therapy in children.⁵

MICROBIOLOGY

The list of bacteria reported to have caused empyema include streptococcal species, *Staphylococcus aureus*, *Haemophilus influenzae*, *Mycobacterium* species, *Pseudomonas aeruginosa*, anaerobes, *Mycoplasma pneumoniae*, and fungi. Pneumococcal infection remains the most

common cause in the developed world, and *Staphylococcus aureus* continues to be the most common organism isolated in children from South Asia.¹⁴ The reported isolation of bacterial causes of empyema from blood or pleural fluid varies widely, from 8–76%.^{15–18} The reasons for this probably reflect antibiotic treatment early in the course of the disease, prior to attempts to culture bacteria. The identification of bacteria has increased with the development of molecular techniques such as the polymerase chain reaction (PCR). One such technique utilizes PCR to detect the unique sequences in bacterial 16S ribosomal DNA (rDNA) genes. Using this technique, Saglani et al. compared 16S rDNA PCR results against pleural culture in 32 samples.¹⁹ Twenty-two were positive for 16S rDNA PCR, compared to 6 culture-positive. One child had a culture-positive result with a negative 16S PCR, but of those 22 PCR-positive, 17 were culture-negative. Importantly, they found 100% concordance for organisms identified by pleural fluid culture and using 16S PCR. Only fully penicillin-sensitive *Streptococcus pneumoniae* was isolated, suggesting that the increase in incidence of empyema is not due to the emergence of penicillin-resistant strains. Using PCR to detect pneumococcal DNA and subsequently performing enzyme-linked immunosorbent assays, Eastham et al. identified type-specific pneumococcal capsular polysaccharides in 32 of 43 culture-negative pleural fluid specimens.²⁰ They demonstrated that most of the cases were due to the type 1 serotype, similar to what was found in the US.^{4,21} Interestingly, the 7-valent pneumococcal vaccine, introduced in the US in 2000, does not protect against type 1, which does not fully explain why the incidence of pneumococcal empyema has been reported to be decreasing in some areas of the US since the introduction of the vaccine.^{7,22}

Margenthaler et al. reviewed the outcome of 110 children who presented with community-acquired pneumonia in St. Louis, Missouri.²³ Organisms were identified in three quarters of all cases, but a worrying finding was that in those children who had a more complex course, only 33% had bacteria sensitive to first-line antibiotics, suggesting that a high proportion of community-acquired pneumonia was caused by resistant bacteria. Molecular techniques, such as PCR, will be useful in the future to monitor the prevalence of bacterial subtypes and the emergence of antibiotic-resistant strains, and to guide appropriate antibiotic treatment.

PRESENTATION

Most children will present with a history of malaise, lethargy, and fever early on in the disease. They proceed to develop cough and tachypnea due to the underlying pneumonic process. Pleural pain and occasional abdominal pain may be features. Occasionally there is a history of varicella infection in the preceding few weeks. As the

empyema progresses, the child becomes increasingly unwell, with swinging fevers and increased dyspnea. Scoliosis toward the affected side is not uncommon, and is visible clinically and on chest X-ray. This occurs initially in an attempt to reduce the pleural pain, but it also may be the result of contraction of the pleural lining on the affected side. Similarly, children may lie on the affected side in attempt to splint the chest. Examination may reveal reduced air entry and dull percussion over the affected side.

INVESTIGATIONS

Serum

An initial blood count may reveal anemia, leukocytosis, and thrombocytosis. Malignancy should be suspected if white-cell counts are normal. There is no place for routine blood investigations in the management of empyema, apart from blood cultures.⁵ Acute-phase reactants such as an erythrocyte sedimentation rate and C-reactive protein (CRP) are unable to distinguish between viral and bacterial infections. However, similar to white-cell counts, CRP may be useful to assess progress in patients who remain pyrexial and are slow to recover. As discussed above, blood cultures are not often positive but are worth sending. Serum may also be sent for molecular techniques to detect organisms, if available.

Radiological

All patients should have a chest X-ray initially to help confirm the presence of pleural fluid and exclude other conditions such as an underlying malignancy (Fig. 1) or lung abscess (Fig. 2). There is no role for routine daily X-rays, as changes lag behind clinical status, and it may take some months for X-ray changes to return to normal, despite a resolution of clinical symptoms.²⁴ The most useful radiological intervention is an ultrasound of the chest. This helps differentiate solid lung from overlying fluid in the case of a “complete white-out” on chest X-ray. It will also detect loculations and fibrin strands, and will help estimate the size of the effusion. Furthermore, the radiologist can mark the spot for chest-tube insertion by the physician or surgeon. In some centers, radiologists insert chest drains under sedation. It was suggested that ultrasound is useful to stage the disease in children.²⁵ However, in a study in adult patients, ultrasound was unable to identify the stage of disease, using Light’s criteria as gold standard.⁶⁵ Again, we emphasize that caution must be taken when interpreting this paper in an adult population, as Light’s criteria have not been fully evaluated in children, and it is difficult to know whether this paper is applicable to the pediatric population.

The role of routine computerized tomography (CT) is controversial. CT is not good for identifying loculations,

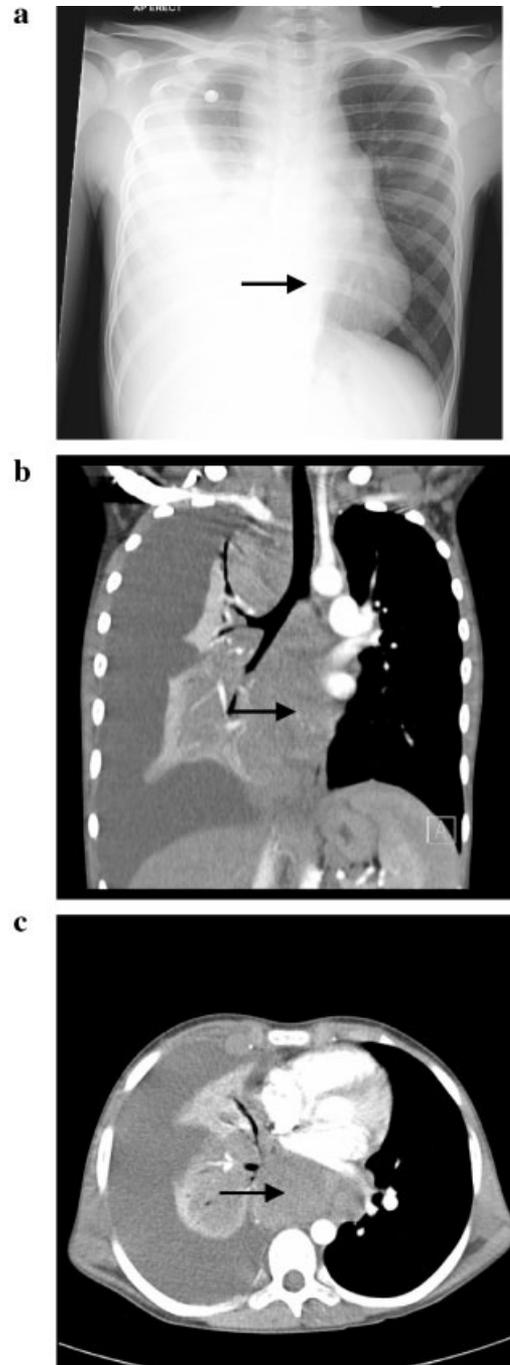


Fig. 1. Non-Hodgkin lymphoma presenting as pleural effusion. Abnormal mass (arrow) is present on chest X-ray (a). This was confirmed on multislice CT scan (arrows; b, sagittal view; c, coronal view).

and is not useful for differentiating simple parapneumonic effusions from empyema in children.²⁶ Some surgeons will insist on a CT scan as a “road map” prior to surgery. In a review of the use of CT scanning in pediatric chest disease, Coren et al. found that CT scans were least useful in the preoperative assessment of empyema complicating community-acquired pneumonia.²⁷ The BTS guidelines

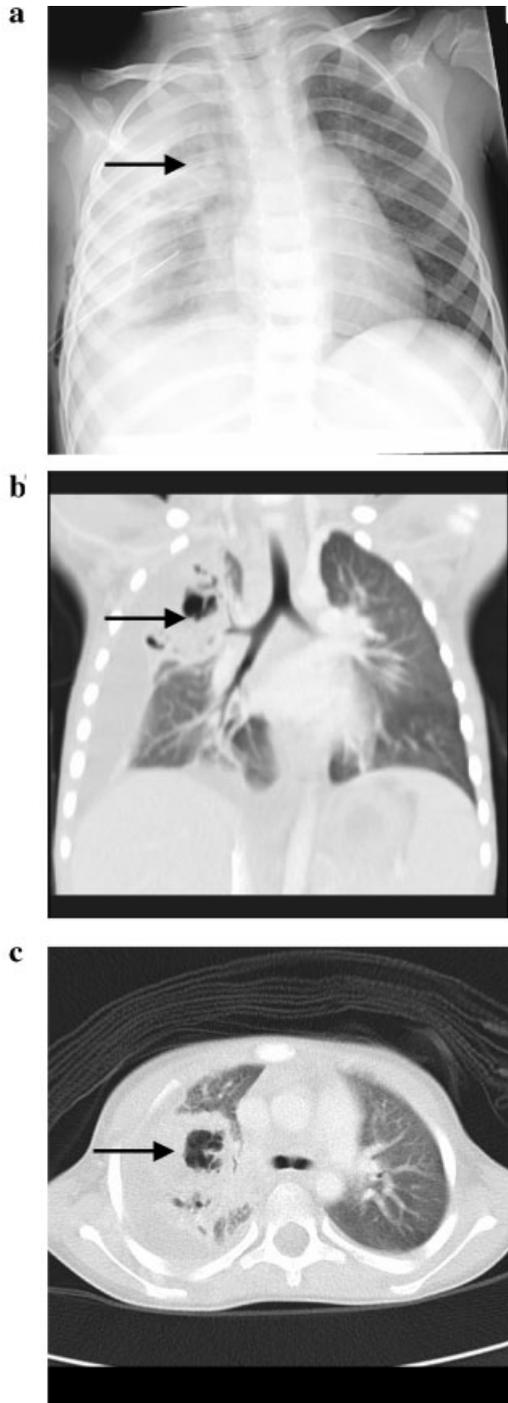


Fig. 2. Empyema complicated by lung abscess. Chest X-ray (a) suggested suspicion of lung abscess (arrow). This was confirmed on multislice CT scan (arrows; b, sagittal view; c, coronal view).

recommend that CT scans should not be done routinely (based on grade D evidence, i.e., expert opinion), but there may be a place for them in atypical empyema presentations, e.g., it is mandatory when there is a concern regarding an underlying tumor (Fig. 1) or lung abscess

(Fig. 2). It may be reassuring when there is an unexpected delay in recovery, e.g., to exclude an underlying lung abscess not present on chest X-ray.

Pleural Fluid

All pleural fluid should be sent for microbiology and molecular techniques if available. Fluid should be additionally cultured for *Mycobacterium tuberculosis*. Cytology is useful, and a cell differential should always be sent, as lymphocytosis (rather than neutrophilia) may indicate tuberculosis (TB) or malignancy.⁵ While a high LDH, and low glucose and protein, may help confirm the diagnosis of empyema, there is no evidence to support their role in guiding management in children as exists in adults, as the presence of pus makes the diagnosis obvious. Furthermore, routine aspiration of pleural fluid will cause unnecessary discomfort and sedation with little perceived benefit. In adults, biochemistry is routinely used on fluid obtained by a tap to guide whether a drain is necessary, a situation that is not usually applicable to children,¹¹ but its role remains to be formally evaluated. An important practical point to bear in mind is that children with superior mediastinal obstruction related to malignancy are at risk of sudden death if they undergo large-volume aspiration and general anesthesia. Thus, in these circumstances, small-volume taps and avoidance of general anesthesia and sedation are recommended.⁵

OUTCOME MEASURES

Comparisons of published studies are difficult for a number of reasons. Firstly, the diagnosis and staging of empyema in these studies are not rigorous. Further, the lack of diagnostic and prognostic markers in pleural fluid and detailed imaging makes comparisons difficult. Because empyema is not one disease, but evolves over time, it is likely that different management strategies may be appropriate at different stages, although there are no data to support this statement. Secondly, the differences in protocols make comparisons problematic. The different fibrinolytic agents used in various studies exemplify this. Thirdly, outcome measures differ between studies. Most published studies used length of stay as the primary outcome measure, while others used radiographic resolution.²⁴ Lung function is another outcome, but it is possible that no differences would be detected between treatment groups if it was the sole outcome, as recovery in children is usually very good. Kohn et al. reviewed lung function in 36 children following treatment for empyema.²⁸ Three months following treatment, 91% demonstrated a restrictive pattern. However, most patients had normal lung function when tested after a year following discharge. While other studies demonstrated obstructive lung function, patients were asymptomatic, with normal exercise tolerance.²⁹

Outcome measures in adult trials cannot be applied to trials in children. A recent multicenter study of streptokinase in adults highlighted the differences between adults and children with empyema.³⁰ In that study, 454 adult patients were randomized to receive 3 days of intrapleural streptokinase or placebo. The primary outcome measures were death or requirement of surgical intervention within 3 months. There were no significant differences between groups in any of the outcome measures, proving the lack of benefit of streptokinase. Approximately 30% of patients died without surgery in both groups, compared to one child's death in all the studies discussed in this State of the Art. Thus outcome measures in adult studies are centered on the short term, whereas in children, they must include long-term outcomes. Future studies in children need to incorporate outcome measures that address health economics, pain and quality of life scores, body image in relation to scars, and length of hospital stay and long-term assessment of lung function.

TREATMENT OPTIONS

The aim of treatment is simple: to stop sepsis and restore pleural fluid circulation, thus restoring normal lung function. In order to achieve this, the pleural cavity needs to be sterilized, and the lung allowed to expand as much as possible. Clearly the first step is to stabilize the child with fluid boluses if required, and give oxygen therapy, antipyretics, and analgesia. The specific treatment regimens available are: antibiotics alone or in combination with thoracocentesis; chest-drain insertion; chest drain and fibrinolytics; open decortication; and video-assisted thorascopic surgery (VATS). The treatment a child currently receives is usually the result of local practice. Variation in practice is partly due to the lack of randomized controlled trials,³¹ due to the fact that children virtually always recover, irrespective of the treatment they receive. The BTS guidelines describe only one randomized controlled study which adequately informs management¹⁸ but does not offer guidance on choosing surgical or medical management, as most published data are in the form of case series only.

Antibiotics Alone

The choice of antibiotic is largely guided by local policy on pneumonia guidelines, and reflects whether the infection was acquired in the community or hospital and whether the child is a normal host or has an underlying condition. Generally, broad-spectrum antibiotics are used to ensure adequate treatment of *Streptococcus pneumoniae*, and consideration should be given to antistaphylococcal cover, particularly if pneumatoceles are present. Consideration should be given to treating anaerobic bacteria in children at risk from aspiration, e.g., in cerebral palsy. Discussion with local microbiologists is important in hospitals in areas where bacterial antibiotic resistance is

an issue.²³ Antibiotics alone have a role in small effusions in which the child has no respiratory compromise. If the child fails to respond after 48 hr and there is evidence of an enlarging effusion either on chest X-ray or ultrasound, then the child will need the effusion drained.

Thoracocentesis

While it is routine to perform a diagnostic tap in adults, this is not the case in children, as it requires cooperation or sedation and is therefore technically challenging. In a retrospective review of 67 children presenting to a hospital in Boston, Massachusetts, with parapneumonic effusions treated by primary aspiration or pigtail drain insertion, the group treated by primary aspiration required significantly more interventions.¹² In an open prospective study from Israel, Shoseyov et al. found no difference in outcome measures following a comparison of early chest-drain insertion in 32 children with a group who received repeated ultrasound-guided needle thoracocentesis on alternate days.³² Although the authors concluded that treatment with repeated thoracocentesis is as efficacious as chest drainage and less invasive, it could be argued that in order to minimize the repeated trauma to the child, early chest insertion should be advocated.

Chest-Drain Insertion Alone

As stated above, children usually recover from empyema irrespective of the treatment they receive, providing adequate fluid drainage is achieved. However, the optimal treatment will result in a short hospital stay, minimal scarring, and restoration of normal lung function. These points should be borne in mind when considering the evidence for chest drainage alone, as exemplified by the study of Satish et al.²⁴ They described 14 children treated with intravenous antibiotics and chest drainage alone at a secondary-level pediatric center. Although radiographic resolution was obtained up until 16 months with restoration of normal lung function, the median duration of hospital stay was 14 days (maximum stay, 28 days). No child required surgical intervention, which led the authors to conclude that decortication is not necessary to prevent long-term respiratory complications. However, the prolonged length of hospital stay, when compared to other intervention studies discussed below, has significant health economic implications, and prompted Spencer in an editorial to comment that it is "not time to put down the knife."³³ A similar median hospital stay (14.5 days) was observed in a retrospective study of clinical practice at Great Ormond Street Hospital for Children between 1989–1997.³⁴ During this period, 54 patients were treated. Seven patients were successfully treated with antibiotics alone. However, 47 patients required chest-drain insertion, and of these, 21 required further surgical intervention. It is likely that the discrepancy

between the two studies with regard to the need for further surgical intervention is due to patient referral demographics. Great Ormond Street Hospital is a tertiary referral hospital receiving patients referred from other hospitals, and thus patients were likely to have had the illness for a longer period than those seen by Satish et al.²⁴

Fibrinolytics

The fibrin formation which occurs as the empyema becomes more advanced results in the formation of loculated pockets of pus and fluid, which makes adequate drainage with a single chest drain difficult. The aim of instillation of fibrinolytics into the pleural cavity is to lyse the fibrinous strands and clear lymphatic pores, thus improving drainage. There have been more than 10 published reports on the use of fibrinolytics in children,^{35–49} but only two are randomized controlled trials. The case series reports described the management in more than 300 children using streptokinase, urokinase, alteplase, or tissue plasminogen activator in very different protocols. In these series, the success rate was approximately 80–90%, and it is evident that the use of fibrinolytics is safe, with the major side effect being pain following administration. However, in three case series reported from the same group in Turkey, describing their use of streptokinase and urokinase, pleural hemorrhage and death were reported in one patient following a reported allergic reaction after urokinase instillation.^{45–47} While this severe complication should be noted, it is difficult to know if the patient populations described in these reports are representative of those seen in other developed countries. In our own experience of treating in excess of 100 patients with urokinase, we have never witnessed a severe adverse reaction following the instillation of urokinase. There is only one randomized prospective study of urokinase, undertaken by Thomson et al.¹⁸ This was a 10-center study of 60 patients undertaken on behalf of the British Paediatric Respiratory Society Empyema Study Group. Patients were randomized to receive either 40,000 units of urokinase in 40 ml saline (10,000 units in 10 ml saline if under 1 year old) or 0.9% saline instilled twice a day over 3 days. The urokinase group demonstrated a significant reduction in length of stay in hospital compared to the saline control group (7.4 vs. 9.5 days). Five patients (two in the treatment arm) failed treatment and required surgical decortication. Interestingly, post hoc analysis showed that the patients who received a smaller percutaneous drain had a shorter stay than those who had a larger-bore drain. The trial was not designed to show this effect, and this may have been the result of a center effect. However, a retrospective review by Pierrepont et al. compared the outcomes of children with empyema treated with either a stiff large-bore drain or pigtail catheter, and found that those who had a pigtail inserted had a much

better outcome in terms of length of hospital stay and the need for further intervention.⁵⁰ In the only other randomized controlled study of fibrinolytics, Singh et al. compared the instillation of streptokinase with normal saline in 40 children in India. There was no difference between all outcome measures between groups.⁴⁸

One surgical concern is that patients may be more likely to fail rescue VATS treatment following urokinase, as it was suggested that urokinase causes intrapleural loculations to become very adhesive, and increases the difficulty of the VATS procedure;^{51,52} this may simply be a result of operating at a later stage. While there have been many case series comparing surgical interventions with fibrinolytics, there has been no properly controlled study to compare treatment modalities. One such trial comparing VATS with urokinase is underway at Great Ormond Street Hospital for Children, and is near completion. The development of more specific fibrinolytic treatments such as single-chain urokinase plasminogen activator, which prevents adhesion formations, remains an exciting prospect.⁵³

Surgery

The surgical options are minithoracotomy, open decortication, or VATS. Open decortication involves the removal of the thickened pleural rind and irrigation of the pleural cavity through a large posterolateral scar. A minithoracotomy is an open debridement procedure, but is performed through a smaller incision. VATS is performed through two or three ports made in the chest: one port is utilized for the camera, and the others for grasping instruments, which can be rotated around the ports if required. Insufflation of the chest cavity with CO₂ aids collapse of the lung for better visualization. Interest in the use of VATS for the treatment of empyema in children has been increasing over the past decade. Proponents of VATS suggest that it has the potential advantage over open surgery of limiting the morbidity to skin, muscles, nerves, and supporting structures which occurs following a large surgical incision⁵⁴ and which entails pain, infection, limitation of movement, and cosmetic scarring.⁵⁵ Furthermore, VATS may reduce cytokine responses compared to conventional surgery.⁵⁶ However, these statements are based on clinical experience rather than controlled trials.

Proponents of open decortication cite evidence which demonstrates that those who undergo that procedure recover more quickly. In a review of 18 patients who underwent primary open decortication, the median stay in hospital was 4 days,²⁵ significantly shorter than for those in a urokinase trial (7.4 days) and those treated by chest drain only (median stay, 14 days). The authors concluded, somewhat controversially, that fibrinolysis and VATS had no place in stage III empyema. As they had not directly compared these treatment modalities, this statement is unfounded. Karaman et al. compared 30 children with

empyema who were randomized prospectively to receive open thoracotomy or chest tube.¹³ Average length of stay in the open thoracotomy group was 9.5 days, compared to 15.4 days in the chest-tube group. This length of stay in the open thoracotomy group was similar to that seen in the urokinase study by Thomson et al.¹⁸ Alexiou et al. reviewed their practice in 44 children undergoing open decortication for empyema, demonstrated a good outcome, and concluded that open thoracotomy remains an excellent option for late-stage empyema, and that VATS or fibrinolysis should be considered on their own merits, and not on the basis of adverse outcomes following open thoracotomy.⁵⁷ In a retrospective comparison of treatment in 48 children, Hilliard et al. reported that those who had a chest drain alone had a median stay of 15 days, compared to 8 days for fibrinolytic therapy and 6.5 days for thoracotomy.⁵⁸ Three children in the chest-tube group and 2 in the fibrinolytic group required subsequent thoracotomy.

As with other treatment options, there are currently no properly controlled studies to inform the use of VATS.³¹ While VATS was initially used as rescue therapy following the failure of medical treatment, it is being increasingly used as primary therapy. In a review of treatment options available to 139 patients at their center in Dallas, Doski et al. demonstrated that those patients undergoing primary VATS had a significantly reduced number of procedures and length of stay compared to those who had secondary VATS or open decortication for failed medical treatment.⁵⁹ Cohen et al. compared outcomes following the introduction of primary VATS in 21 children with at least stage II empyema with a historical control group treated by chest drainage alone.⁶⁰ There was a significant reduction in days in hospital (7.4 vs. 15.4) and chest-tube drainage (4.0 vs. 10.2) in the VATS group. Furthermore, 39% of patients treated with chest drain only required further surgical intervention, compared with none in the VATS group, suggesting that VATS is superior to chest drain alone. These results are similar to those reported from other centers.⁶¹ There are no studies that directly compare primary VATS with open decortication in children. Subramaniam et al. demonstrated a reduced stay in hospital in the VATS arm compared to open thoracotomy in those referred following the failure of medical management.⁶² Gates et al. carried out a systematic review of 44 retrospective studies to assess whether VATS was superior to chest drainage alone, fibrinolysis, or thoracotomy.⁴⁴ VATS and open decortication led to a shorter stay in hospital, but the study highlighted again the lack of properly designed studies. Furthermore, the availability of local surgical expertise and the surgeon's own preference, together with available resources and training, limit the surgical options available to each center, even when evidence supports a particular surgical technique.^{63,64} We now need to obtain compelling evidence (if it exists) so that a case can be made for

ensuring that treatment resources are available, but until then, it is not easy to justify the potentially large expenditure that many centers would require.

CONCLUSIONS

The incidence of empyema continues to rise and cause significant morbidity in children. Despite this, there is little evidence to inform the best management approach, due to a dearth of properly controlled clinical trials. In addition, there is a need for proper microbiological surveillance, and newer molecular techniques may be useful to help guide appropriate antibiotic treatment. The development of specific chemicals to prevent adhesion formation, such as single-chain urokinase plasminogen activation, is an exciting prospect. Until we obtain better evidence to guide management, the children we treat continue to be the victims of our own personal opinions. As Hippocrates pointed out, "there are in fact two things, science and opinion; the former begets knowledge, the latter ignorance." It is high time we became less ignorant.

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