REVIEW

Empyema Thoracis

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Abstract: Epmyema thoracis is associated with high mortality ranging between 6% to 24%. The incidence of empyema is increasing in both children and adults; the cause of this surge is unknown. Most cases of empyema complicate community- or hospital-acquired pneumonia but a proportion results from iatrogenic causes or develops without pneumonia. Parapneumonic effusions (PPE) develop in about one half of the patients hospitalized with pneumonia and their presence cause a four-fold increase in mortality. Three stages in the natural course of empyema have long been described: the exudative, fibrinopurulent, and organizing phases. Clinically, PPE are classified as simple PPE, complicated PPE, and frank empyema. Simple PPE are transudates with a pH > 7.20 whereas complicated PPE are exudates with glucose level <2.2 mmol/l and pH < 7.20. Two guidelines statements on the management of PPE in adults have been published by the American College of Chest Physicians (ACCP) and the British Thoracic Society (BTS). Although they differ in their approach on how to manage PPE, they agree on drainage of the pleural space in complicated PPE and frank empyema. They also recommend the use of intrapleural fibrinolysis and surgical intervention in those who do not show improvement, but the level of evidence for the use of intrapleural fibrinolysis is not high highlighting the need for more research in this area. A recently published large randomized trial has shown no survival advantage with the use of intrapleural streptokinase in patients with pleural infection. However, streptokinase enhances drainage of infected pleural fluid and may still be used in patients with large collection of infected pleural fluid causing breathlessness or ventilatory failure. There is emerging evidence that the combination of intrapleural tPA/DNase is significantly superior to tPA or DNase alone, or placebo in improving pleural fluid drainage in patients with pleural space infection. A guideline statement on the management of PPE in children has been published by the BTS. It recommends the use of antibiotics in all patients with PPE in addition to either video-assisted thoracoscopic surgery (VATS) or tube thoracostomy and intrapleural fibrinolysis. Prospective randomized trials have shown that intrapleural fibrinolysis is as effective as VATS for the treatment of childhood empyema and is a more economic treatment and therefore, should be the primary treatment of choice.

Keywords: empyema, management, intrapleural fibrinolysis, drainage, surgery

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Introduction

Empyema thoracis, defined as collection of pus in the pleural space, has been recognized since the time of Hippocrates and historically has been associated with high mortality. The mortality rate from empyema thoracis remains high and it ranges between 6%–24%.[1–4] Pleural infection develops in 65,000 patients each year in the United States and the United Kingdom.[5] A significant proportion of pleural space infection complicates community- or hospital-acquired pneumonia. However, a proportion of pleural space infection results from iatrogenic causes; it is also known that pleural infection may develop without pneumonia—so called primary empyema.

Epidemiology of Empyema

In recent years, there has been a surge in empyema incidence in both children and adults the causes of which remain speculative.[6–14] The incidence of empyema in childhood is reported to be increasing in the UK and North America.[6–9,11–13] In an analysis of 1349 admissions for empyema in childhood over an eight-year period in England, the highest increase in incidence was observed in the 1–4-year age group, with a rising trend in admission rates seen in all children.[7] Reasons for this increase in incidence are not fully understood, but may include an increase in pneumonia incidence among the paediatric population. The peak incidence of pneumonia in childhood is in those under 5 years of age,[10] and a rise in pneumonia may plausibly account for the reported rise in empyema. However, a Scottish study reported longitudinal trends in incidence of childhood empyema and pneumonia in Scotland over a 25-year period and has shown that empyema admissions increased after 1998 from 10 per million children per annum to reach a peak of 37 per million in 2005.[11] In the 1–4-year age group, empyema admissions rose in the late 1990s and 2000s from an average of 6.5 per million per year between 1981 and 1998 to 66 per million in 2005. Overall annual admission rates for pneumonia remained unchanged in most age groups and the authors conclude that the rise in empyema incidence is independent of pneumonia.[11]

In the Unite States, empyema associated hospitalizations rose by almost 70% during 2006 among children 18 years of age or less when compared to 1997.[12] This was independent of the rate of hospitalization with bacterial pneumonia and invasive pneumococcal disease which have in fact decreased during the same period. Interestingly, pneumococcal conjugate vaccine did not decrease the incidence of empyema.[12]

Among adults, the incidence of empyema increased significantly by 1.2-fold during a nine-year period between 1995 and 2003 in a North American study.[13] Another study, from Utah in the United States, showed a more than six-fold increase in death rate from empyema during a 4-year period between 2000 to 2004 when compared to death rate from empyema during 1950 to 1975.[14]

Pathophysiology of Parapneumonic Effusions

PPE develop in up to 57% of patients hospitalized with bacterial pneumonias.[5,15,16] The presence of PPE increases mortality in these patients by about three- to six-fold.[15,17] Almost 50 years ago, the American Thoracic Society described three stages in the natural course of empyema: the exudative, fibrinopurulent, and organizing phases.[18] It is best to regard these stages as a continuum and that the development of empyema in association with pneumonia is a progressive process that starts as simple exudation and develops into the organizing phase. Exudative pleural fluid is derived from pulmonary interstitial fluid that is associated with lung infection and inflammation; this fluid crosses the visceral pleura and accumulates in the pleural space and is usually not infected—simple PPE. Simple PPE have characteristic biochemical and microbiological features namely: $pH > 7.2$, $LDH < 1000$ iu/l, $Glucose > 2.2$ mmol/l and no organisms in culture or gram stain. Treatment of simple PPE with antibiotics is likely to be adequate and there is no need for pleural fluid drainage.[19] Some patients go on to develop complicated PPE. In these patients, bacterial invasion of simple PPE accelerates immune reaction leading to further migration of neutrophils and activation of coagulation cascade.[20,21] This favors fibrin deposition and leads to septation of the pleural space. The inflammatory process continues fueled by more bacterial death and phagocytes. This leads to the characteristic biochemical and microbiological changes of complicated pleural effusions namely: $pH < 7.20$,

glucose < 2.2 mmol/l, LDH > 1000 iu/l and possible positive gram stain and/or bacterial culture. This is followed by the organizing phase which may progress to formation of a solid pleural peel.

Bacteriology of Empyema

In most series of patients with community acquired empyema, aerobic bacteria predominate.[22] These include *Streptococcus pneumoniae* and *Staphylococcus aureus*.[22] Aerobic organisms also include Gram negative bacteria such as *Escherichia coli*, *Haemophilus influenza* and *Klebsiella pneumoniae*.[22] Mixed aerobic and anaerobic bacteria are commonly isolated from empyema. The commonest anaerobes are *Bacteroides fragilis*[23] In the United Kingdom bacteria commonly isolated from hospital-acquired empyema include staphylococci, enterobacteria, enterococci and *Pseudomonus aeruginosa*.[24]

Management of Empyema in Adults

There is great variation in the management of patients with PPE.[2,26] The condition causes significant death,[1–4,25] and earlier surveys have reported even higher mortality rates[27] and it may be that modern and timely therapeutic interventions have had an impact in reducing death from empyema. Therefore, the management of PPE is best based on guidelines.[28–30] These guidelines are evidence based and may also take into account expert opinion.[28–30]

Comparison of management guidelines in adults

Two important guidelines for the management of pleural space infection in adults have been published by the BTS and the ACCP.[28,29] These two documents adopted different approaches to the management of parapneumonic pleural effusions. The BTS guidelines are centered around: appropriate antibiotics use, sampling and analysis of all parapneumonic pleural effusions, early chest tube drainage for frank empyema and complicated PPE, consideration of intrapleural fibrinolysis and prompt surgical referral if patients are not improving.[28] A diagnostic algorithm for the management of patients with pleural infection may be found in the BTS guidelines.[28]

The ACCP guidelines, however, adopted a different approach; this is based on an annotated table for evaluating the risk for poor outcome in patients with PPE.[29] Estimates of the risk of poor outcome were based on clinical judgment that, without adequate drainage of the pleural space, the patient with PPE would be likely to have any or all of: prolonged hospitalization, prolonged evidence of systemic toxicity, increased morbidity from any drainage procedure, increased risk for ventilatory impairment, increased risk for local spread of inflammatory reaction and increased mortality.[29] Three variables, pleural space anatomy (assessed by amount of pleural fluid, presence of loculated effusions or thickened parietal pleura), pleural fluid bacteriology (assessed by gram stain and or bacterial culture, or presence of pus), and pleural fluid chemistry (assessed by measuring pleural fluid pH) were used in the annotated table to categorize patients into four separate risk levels for poor outcome: very low risk, low risk, moderate risk and high risk.[29] The ACCP statement supported drainage for patients with moderate or high risk for a poor outcome.[29] Generally, these are patients who have a large amount PPE, loculated effusion or effusion with thickened parietal pleura; or have positive culture or gram stain; or pH < 7.20; or pus in pleural space.[29] Pleural fluid drainage may be done using therapeutic thoracocentesis or tube thoracostomy, but for most patients further treatment would be needed and fibrinolysis, VATS and surgery are acceptable approaches.

For both guidelines documents the evidence for each intervention was graded as: A (controlled trials with consistent results or individual randomized, controlled trials with narrow confidence intervals), B (controlled cohort and case-control series), C (historically controlled series and case series), and D (expert opinion without explicit critical appraisal or based on physiology, bench research, or first principles). It is worth noting that none of the intervention recommendations in both documents reached level A. In the BTS guidelines the highest level of recommendation reached was B in 36% of occasions and in 64% of occasions the level of evidence was C.[28] In the ACCP guidelines the highest level of recommendation reached was C in 60% of occasions and the rest was level D.[29] This highlights the lack of good studies in many aspects regarding the management of empyema and emphasizes the need for more research in these areas.

Antibiotic therapy

Antibiotics should be given to all patients with pleural infection and if possible should be based on pleural fluid culture and sensitivities. Other factors that may affect the choice of antibiotics are the ability of an antibiotic to penetrate in pleural space and the presence of renal or hepatic impairment. In the absence of positive culture results, antibiotics should be chosen to cover the likely organisms that may cause pleural space infection. For culture negative pleural infection, a regimen proposed by the BTS guideline document suggests intravenous cefuroxime 1.5 grams 8 hourly plus metronidazole 500 milligrams 8 hourly or intravenous benzyl penicillin 1.2 grams 6 hourly plus ciprofloxacin 400 milligrams 12 hourly or intravenous meropenem 1 gram 8 hourly plus metronidazole 500 milligrams 8 hourly for community acquired infection. For oral therapy the BTS guidelines document proposes amoxycillin 1 gram 8 hourly plus clavulanic acid 125 milligrams 8 hourly or amoxycillin 1 gram 8 hourly plus metronidazole 400 milligrams 8 hourly or clindamycin 300 milligrams 8 hourly.[28]

For culture negative hospital acquired infection, however, the the BTS guidelines document proposes intravenous piperacillin plus tozobactam 4.5 grams 6 hourly or ceftazidime 2 grams 8 hourly or meropenem 1 gram 8 hourly to which metronidazole may be added at a dose 500 milligrams 8 hourly.[28]

The duration of treatment is variable and depends on patient's response. Provided that there is adequate chest tube drainage long term treatment may not be necessary and treatment for about three weeks is probably appropriate.[28] Antibiotics may be changed to the oral route after sepsis has settled.[28]

Chest tube drainage

Traditionally large bore chest tubes have been recommended in empyema to facilitate drainage of thick pus. However, several published studies relate to the use of image guided small catheters and suggest they have good primary outcome.[31–33] Image guided small catheters have the advantage of draining loculated pleural space and have shown success as rescue procedures as well.[31–33] There are no controlled trials comparing large bore chest tubes to smaller catheters. Prompt tube drainage is recommended and is best done at the time of diagnostic sampling as delayed tube insertion has been associated with

poorer outcome in retrospective human studies and a propective experimental animal model.[4,26,34]

Intrapleural fibrinolytic therapy

Intrapleural fibrinolytic therapy was first used more than 60 years ago.[35] The aim of this therapy is to lyse the fibrinous septations within infected pleural space. Following the initial trial of intrapleural fibrinolytic therapy, there was a 32-year gap until the second study was published in 1981 mainly to address the effect of intrapleural streptokinase on systemic fibrinolysis;[36] it may be that concerns about side effects have led intrapleural streptokinase to fall out of use during that period. Since 1981several observational series and fewer controlled trials have been published.[28,29,37,38] The principal end points in these studies were amount of fluid drained, either as absolute volume or as quantified by radiological improvement, and need for surgery. However, these studies have many limitations: first, many are observational uncontrolled trials the limitations of which are obvious;[39] second, measuring the amount of pleural fluid drained may be deceptive as intrapleural streptokinase may induce pleural fluid accumulation;[40] third, they did not have the statistical power to measure primary end points of clinical interest such as patient mortality, need for surgery and residual lung volume.[39] Clinical evidence of a benefit, therefore, remains marginal. Reviews performed by the Cochrane Collaboration describe existing data as incomplete and results should be treated with caution as the benefit of intrapleural fibrinolytic therapy is not significant in the subgroup of high quality studies.[41]

Recently, a large United Kingdom multi-centre double-blind trial including 454 patients with pleural infection was published. Patients were randomly assigned to receive either streptokinase (250,000 units twice daily for three days) or placebo.[42] The primary end points were death or need for surgical drainage at three months. The secondary end points were rates of death and surgery (analyzed separately), the radiographic outcome, and length of hospital stay. There was no significant difference between the groups who received streptokinase or placebo as proportion of those or died or needed surgery: relative risk, 1.14; (95% confidence interval 0.85 to 1.54; $P = 0.43$).[42] Regarding the secondary end points, there was no benefit to streptokinase in terms of mortality, rate of surgery, radiographic outcome, or length of

hospital stay.[42] Serious adverse events including chest pain, fever, or allergy were more common in those who received streptokinase.[42] These findings has led the authors conclude that fibrinolytic therapy should generally be avoided in pleural infection.[42] However, it is important to remember that this study was not designed to readdress the effectiveness of streptokinase in reducing the volume of infected pleural fluid collections as this has been established in previous studies.[37,43] Therefore, there may still be a place for intrapleural fibrinolysis in treating some patients in whom large collection of infected pleural fluid causes shortness of breath or ventilatory failure.

Intrapleural DNase

Although streptokinase lyses adhesions, it does not reduce pus viscosity.[44] It is possible that combination of agents that reduce pus viscosity and break down loculations may be more effective in draining infected pleural space. Recently there has been an interest in intrapleural DNase as a possible candidate in combination with thrombolytic therapy to enhance pus drainage.[44] In an animal model, the combination of recombinant tissue plasminogen activator (alteplase) and recombinant human deoxyribonnuclease (rhDNase) has been shown to be more effective in treating empyema than either agent used alone.[45] Successful treatment of human empyema with intrapleural rhDNase given after intrapleural fibrinolytic therapy has been described in at least one case report.[46]

A multi-centre randomized trial of intrapleural tissue plasminogen activator (tPA) and DNase in pleural infection has recently been completed but is currently only reported in abstract form.[47] Two hundred and ten patients with pleural space infection were randomized to receive: double matched placebo, active tPA plus active DNase, active tPA plus placebo DNase, or placebo tPA plus active DNase for 3 days. Combination intrapleural tPA/DNase was significantly superior to the other combinations in improving pleural fluid drainage. DNase alone appears to be associated with increased frequency of surgery/death. The proportion of patients dying or requiring surgery for their infection was higher in the DNase plus placebo group and similar in all other groups (number of deaths or surgery tPA/DNase 17.3%; placebo/placebo 12.7%; tPA/placebo 15.4%; DNase/placebo 45.1%, X^2 3, $P = 0.0001$).[47] A peer reviewed full report of this trial is eagerly awaited.

Surgical treatment

Many surgical techniques have been employed in the treatment of empyema including debridement via VATS, decortication, thoracoplasty and open window thoracostomy.[48] Debridement via VATS has gained popularity from the mid 1990s,[49] and its Success rate ranges from 68% to 93%.[48] The success rate of VATS debridement very much depends on the stage of PPE and the more patients in the organizing phase the higher the failure rate.[50]

Decortication is the method of choice when the underlying lung is unable to expand due to the thick inflammatory coat and the patient is fit for major surgery.[51] Decortication has been shown to substantially improve both vital capacity and forced expiratory volume in the first second.[52] Thoracoplasty entails remodeling of the osteomuscular wall of the thoracic cage in order to control the underlying inflammatory process but is rarely done these days.[48] Another operative procedure—open window thoracostomy—is performed in debilitated patients when thoracoplasty is not an alternative and when VATS has failed to control the disease. It can be done as a definite procedure with intent to cure, as a last resort procedure when other treatment has failed to achieve a relatively stable state or as a preliminary procedure prior to definite treatment.[48,53]

Management of Empyema in Children

The principal difference between adult and paediatric empyema is that, since it is rare for children to have an underlying lung disease, the prognosis with treatment is almost always excellent.[30] The BTS published an important separate guidelines document for the management of pleural space infection in children.[30] In this document the management of empyema is planned according to an algorithm. The algorithm recommends that all children with a clinically suspected parapneumonic effusion or diagnosed pneumonia with treatment failure over 48 hours should have chest radiographs and if these radiographs show features of pleural effusion this should be confirmed by chest ultrasonography. Intravenous antibiotics should be given to all patients. In addition patients should receive either medical treatment in the form of chest tube drainage with pleural fluid sampling for microbiology at the same time of chest tube insertion or early surgery in the

form of VATS or mini-thoracostomy. For those who were treated medically, if they were noted to have loculated pleural space or thick pus they should be candidates for intrapleural fibrinolysis. If patients do not improve after intrapleural fibrinolysis they should be referred for late surgery. For those who improve after chest tube drainage or surgery intravenous antibiotics may be changed to the oral route and continued for one to four weeks.[30]

The BTS guidelines document for the managent of pleural space infection in children grades the level of evidence for each intervention. A remarkable finding is that, like the adult guidelines documents, the level of evidence for interventions is low. It is worth noting that none of the intervention recommendations in the BTS guidelines document for the management of pleural space infection in children reached level A. The highest level of recommendation reached was B in 7% of occasions and in 12% of occasions the level of evidence was C and the rest was level D.[30] This emphasizes the need for more research in these areas.

Two prospective randomized trials compared thoracoscopic decortication to tube thoracostomy with fibrinolysis for empyema in children.[54,55] Their findings were similar. Sonnappa et al randomized 60 children with empyema to receive either percutanous chest drain with intrapleural urokinase or primary VATS.[54] No significant difference between the two groups was found in length of hospital stay after intervention, total hospital stay or radiological outcome at six months after intervention. However, the treatment costs for patients in the urokinase arm were significantly lower than those for the VATS arm.[54] St. Peter et al studied a total of 36 patients who were randomized to receive either three doses of 4 milligrams each of tissue plasminogen activator via a 12F chest tube or decortication via VATS.[55] There was no difference of days of hospitalization after interversions, days of oxygen requirement, days until afebrile, or analgesic requirements. VATS was associated with significantly higher charges. Three patients in the fibrinolysis group subsequently required VATS and two in the VATS group required ventilator support one of whom required temporary dialysis.[55] It can be concluded from these two studies that there is no difference in clinical outcome between intrapleural fibrinolysis and VATS for the treatment of childhood empyema. Intrapleural fibrinolyis is a more economic treatment option compared with VATS and should be the primary treatment of choice in children.

Conclusion

Empyema thoracis is a cause of high mortality in man and its occurrence is increasing in both children and adults. Two guidelines documents on the management of empyema in adults have been published by the ACCP and the BTS. Although they differ in their approach to management, they agree on that the pleural space should be drained in all patients with exudative PPE with pleural fluid pH < 7.2 and in those who have frank pus in the pleural space. Patients who do not improve should be referred to the surgeon for further management. A large randomized multi-centre trial has shown no survival advantage with the use of intrapleural streptokinase in patients with pleural infection and the use of streptokinase has not prevented surgery in the group of patients studied. However, streptokinase enhances infected pleural fluid drainage and may still be used in patients who have large collection of infected pleural collection causing ventilatory impairment. There is emerging evidence that combination of intrapleural tPA/DNase is significantly superior to tPA or DNase alone, or placebo in improving pleural fluid drainage in patients with pleural space infection. A guideline document on the management of PPE in children has been published by the BTS. It recommends the use of antibiotics in all patients with PPE in addition patients should be treated by either VATS or tube thoracostomy. For those who received tube thoracostomy if there is thick pus or loculation of pleural space the guideline document recommends the use of intrapleural fibrinolysis. Prospective randomized trials have shown that there is no difference in clinical outcome between intrapleural fibrinolysis and VATS for the treatment of childhood empyema. Intrapleural fibrinolyis is a more economic treatment option compared withVATS and should be the primary treatment of choice in children.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not

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