ABSTRACT

Objectives
Pleural infection is a condition commonly encountered by the respiratory physician. This review aims to provide the reader with an update on the most recent data regarding the epidemiology, microbiology and the management of pleural infection.
Data source
Medline was searched for articles related to pleural infection using the terms 'pleural infection', 'empyema' and 'parapneumonic'. The search was limited to the years 1997-2017. Only human studies and reports in English were included.
Results
A rise in the incidence of pleural infection is seen worldwide. Despite the improvement in healthcare practices, the mortality from pleural infection remains high.. The role of oral microflora in the aetiology of pleural infection is firmly established.
A concise review of the recent insights on the pathogenesis of pleural infections is presented. A particular focus is made on the role of tPA, DNAse and similar substances and their interaction with inflammatory cells and how this affects the pathogenesis and treatment of pleural infection .
Conclusion
Pleural infection is a common disease with significant morbidity and mortality, as well as a considerable economic burden. The role of medical management is expanding thanks to the widespread use of newer treatments.

Keyword: pleural effusion, infection, computed tomography, clinical epidemiology, thoracic surgery, biomarker

INTRODUCTION

A doubling in the incidence of hospitalization with empyema in the United States was seen at the end of the last decade[1]. This trend is being seen throughout the age spectrum from healthy young adults, to older patients with comorbidities. The estimated annual costs mount to $US500 million[2] in adults alone. This disorder was described over five thousand years ago and has claimed many lives, the most high profile including William Osler and Guillain Dupuytren. Clinical outcomes remain poor with up to 20% requiring surgery and one in five patients dying within the first year of diagnosis. This figure is as high as 30% in the frail and elderly, a constantly growing population, as well as the immunocompromised. Recent years have seen a better recognition of the microbiology responsible using genetic techniques such as nucleic acid amplification testing, and this in turn has led to a greater understanding of the underlying pathophysiology. Although it had been previously assumed that pleural infection was an extension of lung parenchymal infection, bacterial links with oral commensals and gastric aspiration have recently been recognized. Whilst

the main aims of treatment continue to be drainage of the pleural fluid, antibiotics and optimising nutrition, the advent of intrapleural tPA and DNAse has been a major advance in the non-surgical treatment of pleural infection[3]. The theory that tPA breaks adhesions while DNase reduces pus viscosity is probably an oversimplification. Complex interactions of tPA and DNase with bacteria, as well as resident and inflammatory cells within the pleural space are likely to form the basis for novel biomarkers and newer therapeutic targets.
This review aims to provide an update on the most recent data regarding different aspects of diagnosing and treating pleural infection.

Data source

A search was performed on Medline for articles related to pleural infection using the terms 'pleural infection', 'empyema' and 'parapneumonic'. The search was limited to the years 1997-2017 and only human studies and reports in English were included. Data on the trends in incidence and mortality of pleural infection were extracted as well as the bacteriological profile and pathogenesis of the disease, and the different treatment approaches.

HISTORY

Although the last two decades have seen great progress in our understanding of pleural infection, this is by no means a modern condition. The earliest report of empyema is credited to the Egyptian physician, Imhotep, in around 3000 BC. Around 500 BC, Hippocrates gave a clearer description of the disorder, including treatment with open thoracic drainage[4]. This remained the mainstay of treatment until the first World War, which coincided with the influenza epidemic and the resultant crisis of streptococcal pneumonia and empyema[5]. This led to the experimental practice of closed chest tube drainage. To the best of our knowledge, closed water-seal chest drainage was first illustrated in 1873 by Playfair[6]. This was shortly followed in 1875, when a German internist Gotthard Bulau outlined how he treated an empyema by puncturing the pleural membrane with a trocar, introduced a rubber catheter into the pleural cavity, and then attached the free end of the catheter to a bottle one-third full of solution, allowing pus to flow freely from the pleural space into the bottle[7]. The three-chamber thoracic drainage system, which forms the basis of our chest drains today, was first described by Howe in 1952, and this became standard of care from the end of that decade[8,9].

EPIDEMIOLOGY

It is estimated that more than 80,000 patients are diagnosed with empyema in the US each year.[10,11] Empyema leads to long hospitalisation, which varies between a median of 12-21 days of hospital stay according to different studies.[12,13]
An increase in incidence of pleural infection as well as a shift in age distribution towards more elderly patient is consistently reported[12–14]. The overall incidence is

about 9 per 100 000.[14] A study looking at pleural infection in Canada between 1995-2003 found that incidence in the age bracket 20-40 years was 2-6 per 100 000 while it was found to be 19 per 100 000 in those between 75-79 years.[13] In another study in Taiwan looking at incidences between 1999-2008 an increase of the proportion of patients >65 years old by 9.5% was seen.[14]

Due to advancing age, patients with pleural infection are inevitably complex due to the high prevalence of comorbidities. An estimated 40-58% of patients are found to have at least one comorbidity.[14,15] The disease is associated with relatively high mortality rate which varies considerably according to the age. The 30-day in-hospital mortality rate is in the vicinity of 2-7% in adults below 45 years old which rises steeply to between 20-25% in patients older than 75 years.[14,15] In a century-long view of empyema mortality trends in the state of Utah,[16] the highest rates were noticed during the Spanish Flu pandemic. The levels plummeted to a nadir of 0.3 deaths per 10,000 person years towards the 1950s, but then surged during the first decade of the 21st century where it rose six-fold.[16]

PATHOGENESIS

Despite the common view that empyema is the more advanced and challenging phase of pleural infection[11], patients with purulent pleural collections have been noted to have better outcomes.[17] This suggests that the presence of loculations, rather than the purulence of the fluid may be related to failure of treatment.

Fibrin is normally not present in the pleural space, but pleural injury is associated with florid fibrin deposition.[18] Extravascular migration of fibrin, in the course of pleural inflammation, followed by interaction with components of the fibrinolytic systems as well various proinflammatory and profibrtic mediators leads to deposition of firm meshwork of loculation and the transformation of the simple pleural space to a complex one.[18]

The pathobiology of pleural infection involves complex interplay between different cells of immunity, mediators of inflammation, the coagulation cascade and the offending organism(s), only a small part of which we understand thus far .[19] The pathophysiological model for pleural infection mainly describes the sequence of events from aspiration of oropharyngeal flora into lung parenchyma where infection ensues to invade the pleura space. These stages do not necessarily happen in primary pleural infection, where the organism spreads via the haematogenous route. This does not take into account cases with post traumatic empyemas (secondary to infected haemothorax) and direct extension of infection to the pleura from extrapulmonary sources.

The invasion of micro-organisms to the pleural space causes a heavy influx of inflammatory cells and cytokines with activation of the coagulation cascade.[11,18] A key component of this phase is the cleavage of plasminogen into plasmin by substances such as tissue plasminogen activator (t-PA) which competes with inhibitory substances such as plasminogen activator inhibitors (PAI)-1 and -2.[18] The outcome of this interaction defines how complex the pleural space becomes.

This interaction is amenable to medical intervention (see below). Lipoteichoic acid (LTA), a surface molecule found on gram positive bacteria, was found to cause upregulation of PAI-1 expression in mesothelial cells.[20] Whether this is an 'inhibitable' target that can play a role in hampering fibrin deposition in the infected pleural space is yet to be explored.

The MIST-2 trial showed that combined intrapleural tPA and DNase enhanced the drainage of infected pleural effusion.[21] Later, Lansley et al theorised the injection of t-PA itself is a stimulus for pleural fluid production.[22] Their experiment on mice revealed that tPA induced pleural effusion formation which was driven by monocyte chemotactic protein-1 (MCP-1). They also found that MCP-1 antagonists potently inhibit the large effusion formation following intrapleural fibrinolysis[22].

It is know that the microbiology of community-acquired pleural infection is different from that of community-acquired pneumonia. Atypical pathogens that cause large proportions of CAP are virtually non-contributory to pleural infection.[23] This might be related to the different affinities of organisms to settle in the pleural space whose environment, in terms of oxygen content and prevailing pH, is very different from the lung parenchyma.[11] Lending support to this theory, it was recently found that Streptococcus pneumoniae, but not other organisms, grows in pleural effusion much faster than on a culture plate.[24]

MICROBIOLOGY

The microbiological niche of pleural infection varies according to the geographical location,[25,26] as well as the infection setting whether it is community-acquired (CA) or hospital-acquired (HA).[27–29] Age (adults vs children) and immune status both contribute to the variation.[11,30]

Table 1 summarises the prevalence of different bacterial groups and organisms, as causative agents in CA and HA infection. The high prevalence of anaerobic organisms as well as the facultative anaerobic Viridans streptococci sheds light on how the pleural milieu favours the flourishing of these organisms; many of which are either commensals of the oral cavity or responsible for oral/dental infections. In studies focusing on the anaerobic pattern of bacterial infection, anaerobic or micro-aerophilic organisms were isolated with more than 70% of samples from infected effusions.[31] Almost a quarter of these samples isolated 3 or more organisms,[31] stressing the fact that in many cases, the pleural space becomes co-infected by multiple organisms.

Streptococcis milleri group (a subgroup of Viridans streptococci) has been found to be the most prevalent organism in CA pleural infection worldwide.[26–29] In reports from the Far East, Klebsiella species appear to be most common, especially in HA infections.[25,26,29] The latter observation is likely related to the high prevalence of pyogenic infections caused by Klebsiella in this part of the world.[15]

Staphylococcal infection is very common both in the CA and HA setting, with a notable increase in the share of methicillin-resistant organisms in the HA setting

(table 1). Staph aureus infection is particularly common in children where it contributes to the aetiology in up to 50% of cases.[30] In studies by Maskell et al[27] and Asai et al[32], HA pleural infection was associated with higher in-hospital, 30-day and one-year mortality.[27,32] Mortality was also higher when pleural infection was caused by Staph. aureus, gram negative organisms as well as mixed anaerobes.
Identification of the offending organism is not always feasible. The largest series report a positive culture yield on pleural fluid of 40-60% using conventional methods.[25,27–29] When cases are split into HA and CA, the positivity of CA cases was found to be 28%.[29] The more costly nucleic acid amplification tests provide only a modest improvement, as they are able to identify the organism in a further 10-15% of cases, but close to one quarter of the cases have no identifiable causative organism.[27] In a recent study, it was found that the performance of culture and sensitivity tests on pleural biopsies in addition to pleural fluid increased the microbiological yield by 30%.[33]
Empyema due to fungal infection is uncommon, particularly in the immune-competent host. A fungal aetiology for pleural infection was reported in 3% of more than 2000 cases where fungal cultures were carried out (results from unpublished systematic review). In a study examining fungal empyema, Candida species were the most common offending organism, isolated in 68% of cases. In this study, 28% of patients were reported to have a degree of immune suppression.[34]

DIAGNOSIS

Clinical Presentation

Due to the variation in clinical presentation, making a prompt diagnosis of pleural infection can require a high index of suspicion. Physical examination can be suggestive of a pleural effusion but is often unhelpful in specifically identifying pleural infection as the underlying aetiology, where a careful history is of more value. Pleuritic chest pain and dyspnoea are common. When presenting acutely and accompanied by one or more of a fever, cough and sputum production, bacterial pneumonia complicated by parapneumonic effusion is likely, and this is most commonly associated with aerobic bacteria pleural space infection, commonly seen in younger, previously fit, patients. A second group present more insidiously with a subacute illness, and often describe non-specific features of weight loss, fatigue, anorexia or anaemia[35]. Anaerobic bacteria are more likely to be responsible, and patients will usually have some degree of immune compromise, such as alcoholism, poor oral hygiene or frailty. This may indicate failure to recover from a preceding pneumonia, allowing time for bacteria to colonise the pleural space, or a representation of their predisposition to recurrent aspiration. Along with these characteristics, the delayed recognition caused by late presentation, results in a higher morbidity and mortality in this group[36,37]. Clinical prediction scores, such as RAPID[38], which is currently being studied in a large multicentre observational trial (ISRCTN 50236700) to confirm its validity, may enable risk stratification and

outcome prediction at presentation. This was derived from two large prospective randomised trials, which determined that age, urea, albumin, hospital-acquired infection, and non-purulence predicted poor outcome.

Pleural Fluid and Biomarkers

Once a pleural effusion is identified on chest radiograph in the context of infection, there are no clinical criteria that can aid differentiating a complex parapneumonic effusion requiring chest drain insertion, from a simple effusion that one would expect to resolve with antibiotics alone[39]. Pleural fluid characteristics remain the most reliable diagnostic tests to guide management of pleural infection[40] and prompt sampling is recommended in all patients with an effusion with greater than 1cm depth, associated with a pneumonic illness, recent chest trauma, surgery or features of ongoing sepsis[41]. The use of ultrasound guidance is well established as standard of care and strongly recommended in all procedures involving pleural fluid[42,43]. The further benefit of ultrasound lies in differentiating multi-septated effusion, where a small series showed that the biochemistry can differ in sampling different locules. This is particularly useful when a single pleural fluid result appears out of context with the clinical status of the patient and the ultrasound appearance[44]. Fluid biochemistry demonstrating high protein, low glucose <2.2mmol/L and a high LDH >1000 IU/L [41] are consistent with bacterial pleural infection, with the exception of ammonia producing organisms such as Proteus[45], which may prevent the fluid from becoming acidic. To date, the most powerful clinical indicator to chest tube drainage is a pleural fluid pH <7.2, a cut-off universally agreed among international guidelines. The sample for pH should be collected anaerobically in a heparinised blood gas syringe, as the presence of air can falsely elevate pleural fluid pH, as can delay in measurement[46]. Lidocaine is acidic and falsely depresses fluid pH. Visualisation of frank pus on pleural aspiration is diagnostic of empyema requiring chest tube drainage, and does not require any further confirmatory investigation. Microbiological analysis should be requested on all initial fluid samples.

In addition to a universal container, samples sent in blood culture bottles improves the positive culture yield from 40% to almost 60%[47,48]. Although microscopy for acid-fast bacilli in pleural fluid identifies TB in fewer than 10% of cases, this should be requested in patients with risk factors and high risk populations[49]. High pleural fluid adenosine deaminase values are only helpful in differentiating tuberculous from malignant effusions in populations where TB is highly prevalent, or in developing countries, where access to pleural biopsy may be limited by inadequate healthcare resource or cost[50]. Given that some cases of pleural malignancy can mimic pleural infection in their biochemical similarity of low pH and glucose, cytological analysis for cell count and differential is recommended in all cases of suspected pleural infection, with a minimum recommended fluid volume of 40-50ml[51].

Novel infection biomarkers such as CRP, procalcitonin and soluble triggering receptor expressed on myeloid cells (STREM-1) have been evaluated for their use in diagnosing pleural infection and aiding decision on chest tube drainage, but have not yet proven high diagnostic or prognostic value, and as such are not recommended in standard clinical practice[52,53].

Radiology

A standard postero-anterior chest X-ray is frequently the first radiological test requested. It is worth noting that on many occasions, the effusion in pleural infection does not exhibit the meniscus sign due to the presence of encystment, but rather shows a steeply rising line towards the apex of the thorax (figure 1), or even appear as an indistinct opacity that does not obscure the diaphragm shadow (figure 2A). In such instances, thoracic computed tomography (CT) is very useful in deciphering the underlying anatomy.

Thoracic CT is indicated in all cases of pleural infection which are not draining effectively within the first 24-48 hours, and should be conducted with intravenous contrast.[54] Pleural enhancement is one of the key findings denoting active pleural inflammation and is seen both in malignancy and pleural infection. Significant thickening and enhancement of the parietal pleura creates the appearance commonly referred to as the 'split pleura' sign which is highly suggestive of empyema (figure 2B). The finding of extrapleural fat hypertrophy is a valuable marker of a benign inflammatory effusion(figure 2B), including pleural infection.[55] In cases of multi-loculated empyema, complete mapping of the extent of the disease can only achieved by CT. Porcel et al[56] examined CT scans of patient who had pleural infection and found that the presence of air foci inside the fluid, pleural enhancement, estimated fluid volume more than 400 mls and extraplural fat enhancement were predictors of complicated pleural infection.

Thoracic ultrasound is a vital tool in the management of pleural infection. It is superior to CT in the ability of detection of septations(figure 3).[57] In multiloculated collections, TUS helps guide the safe insertion of chest drain in to the largest loculus, which sometimes leads to complete evacuation of the infected fluid, as such loculi are often connected.

TREATMENT

Antibiotics

Antibiotics continue to be the most important initial step in the treatment of pleural infection. These are often started empirically, as approximately 40% [41] will remain persistently culture negative, and indeed, pre-culture systemic antibiotic therapy may be a contributing factor to this. Antibiotic choice is guided by local bacteriology, the clinical setting and the suspected cause of the pleural infection. Treatment should be aimed at gram positive aerobes, commonly attributed to most community

acquired pleural infection, as well as anaerobes, as these organisms have a much lower positive culture yield. In the setting of HA infection, particularly iatrogenic, post-op and trauma-related empyema, the incidence of MRSA is significant and should be adequately covered. The low prevalence of Legionella and mycoplasma in pleural infection does not justify routine cover with a macrolide[58].
Intrapleural antibiotic therapy has been the subject of varied interest over the course of the last decade. This is mainly due to trials with small numbers in the setting of surgically treated empyema,, but not supported by short or long term clinical benefit [59],[60]. Additionally, previous studies have shown the concentration of parenterally administered antibiotics within a parapneumonic effusion are up to 75% of those found in serum[61] Good pleural penetrance has been demonstrated in most antibiotic classes, except for aminoglycosides[41]. The duration of antibiotic therapy in pleural infection has been traditionally extrapolated from lung abscess treatment with most experts advocating a minimum of 4 weeks treatment, and the switch from intravenous to oral being guided by cessation of pyrexia, clinical improvement and resolution of inflammatory markers[39]. A recent cohort study from the Mayo Clinic studying 91 patients over a 10 year period concluded that three weeks of treatment was generally adequate to prevent treatment failure, with prolongation of the initial intravenous course rather than the oral course associated with fewer cases of treatment failure.[62]

General measures

Poor nutrition has been identified as a determinant of poor outcome in pleural infection since the first World War, but despite its presence in guidelines[41], it continues to be frequently overlooked. Clinicians may become absorbed in debates over initiation of intrapleural fibrinolytic therapy and surgical referral, and often fail to appreciate the catabolic consequences of pleural infection, including immunodeficiency and slow recovery[39] One series published almost 3 decades ago, demonstrated that hypoalbuminaemia was the most important determinant of a fatal outcome[63] It is therefore essential that early and adequate nutritional support is provided in all cases of pleural infection, usually via the nasogastric route where required. All patients with pleural infection are at high risk for the development of venous thromboembolism and should receive adequate thrombosis prophylaxis with heparin unless contraindicated[41].

Chest drain

Despite analysis of data from the MIST-1 study having shown that larger bore chest tubes do not positively influence clinical outcomes in pleural infection in terms of the combined frequency of death or need for surgery[64], size continues to be a subject of ongoing debate[65]. The same study demonstrated that the patient experience is significantly improved with smaller bore catheters, due to less traumatic insertion and being more comfortable during the drainage period, a conclusion echoed in malignant pleural effusion data [66]. It is also noteworthy that

the patients who benefitted from tpA/DNase in the MIST-2 study all had chest tubes <15 French [21]. The main reason behind the controversy, other than it seeming logical that high viscosity fluid would drain more easily through a bigger tube, is the lack of high quality data [65] and the frequency with which small tube catheters become blocked. The PIT trial has shown promising evidence that pleural irrigation with normal saline may help overcome this problem [67]. This was a single centre pilot RCT that used 250ml bags of 0.9% sodium chloride administered through a giving set into the thoracic cavity via chest tube and 3-way tap from a drip stand, compared with standard of care 30 ml saline chest tube flushes 3 times a day. Saline irrigation resulted in a 32% reduction in CT pleural volume over 3 days, compared with 15% in the standard care arm, although no significant clear difference in surgical outcome. A large multicentre RCT is now underway to evaluate this further. Long-term chest drainage in combination with prolonged antibiotics is another therapeutic option in those patients with chronic pleural space infection who are not suitable for surgical intervention, due to poor performance status or severe multi morbidity. This can be undertaken through insertion of a wide-bore drain with a one way valve or an indwelling pleural catheter [68,69].

Intrapleural Fibrinolytic Therapy

The theory that the increasing amount of fibrin and density of the septations within the infected pleural space may be the reason behind failure of standard medical treatment, sparked interest in intrapleural fibrinolytic therapy (IPFT). This was described as early as 1949 by Tillett et al using streptokinase, but resulted in significant immunological side effects[70], likely to have been attributed to contamination during production, and was therefore abandoned. Purified streptokinase and urokinase then became available in the late 80's with variable clinical use, and a number of studies over the next 2 decades demonstrated clinical benefit, but only in small studies. A meta-analysis in 2004 concluded that while there was potential benefit from IPFT in pleural infection, this was insufficient to recommend its routine use in clinical practice[71]. The results of MIST-1 were then published in 2005, disproving the pre-existing assumptions and concluded that the intrapleural administration of streptokinase did not improve mortality, the rate of surgery, or the length of the hospital stay among patients with pleural infection [72]. Whilst streptokinase may help break down septations, it was not postulated to alter fluid viscosity or prevent formation of bacterial biofilms in the infected pleural space. Data on cystic fibrosis patients demonstrates that nebulised DNAse is effective in reducing viscosity of secretions and airway clearance[73]. Two laboratory studies, assessing the effects of fibrinolytic and DNase in pleural infection were published in 2000, using samples of purulent pleural fluid and suggesting that DNAse, in combination with a fibrinolytic, could be effective therapy [74,75]. The MIST-2 randomised trial, published in 2011, recruited 210 patients over 3 years from 11 UK centres [21]. It was designed as a double-dummy, double-placebo RCT with 4 arms comparing placebo, tPA alone, DNAse alone and combination tPa and DNAse. The

primary outcome was absolute reduction in CXR opacification, using a validated digital measurement protocol, to exclude interpretation bias. Secondary outcomes included duration of hospital stay, referral to surgery, and death. The study showed combination therapy to have a statistically significant benefit in all of these measures, and confirmed that neither fibrinolytic alone (as in MIST-1) or DNAse in isolation were no better than placebo, proving that it was the combined action of both drugs together that influenced successful drainage of infected pleural fluid. The limited number of patients in the combination arm (52) meant that routine use could not be recommended in all patients, but until larger trials are published, it is limited to being a useful option in cases where standard of care chest drainage has failed where patients are not suitable surgical candidates. Larger trials are now needed to consolidate the safety profile, although case series of more than 100 patients have been published showing no safety concerns and apparently high efficacy (Picolo et al). Bleeding risk continues to be an concern, despite a retrospective review of the MIST-2 data, as well as a number of published studies, reporting no statistically significant increase in bleeding risk[76–81] including a study looking at patients who continued their prophylactic-dose anticoagulation[82].

The dosing regimen for intrapleural tpA/Dnase used in MIST2 was empirically based on earlier case reports. Some recently published pilot data has looked at the effectiveness of dose de-escalation of the MIST-2 protocol, and seems to suggest that halving the dose of tPA to 5mg twice daily intrapleurally with the same 5mg dose of DNase is safe and effective. This regime is yet to be tested in larger RCT's. Despite a similar bleeding incidence, of approximately 6%, , such a regime may help alleviate some of the anxiety surrounding the use of IPFT [83] as well as making it more cost-effective. A small prospective observational study of 38 patients looked to simplify the regime comparing concurrent vs sequential intrapleural instillation of tPA and DNase, removing the 1hr interval between each administration, and reported similar treatment success [84]. Another study changed the frequency to once daily in 55 patients and was able to treat 92.7% successfully without the need for surgical intervention [85]. As well as finding the optimal dosing and administration strategy, an attractive idea in this era of personalized medicine is the question of whether the dose of IPFT can be individualized to different patients. Samples of pleural fluid from the MIST-2 study were found to have highly variable fibrinolytic potential prior to treatment, and it has been stipulated, though not yet clinically tested, that patients with reduced plasminogen activator activity theoretically require higher doses of fibrinolytics[86]. The knowledge that PAI-1 levels are elevated in locules, and therefore likely to contribute to the formation of pleural septations[87], has led to attempts at therapy targeting this specific pathway. PAI-1 targeting monoclonal antibodies could be used as adjunctive therapy to allow reduction in the dose of IPFT and lessen bleeding risk[88]. Similarly, single-chain urokinase-type plasminogen activator (scuPA), a proenzyme fibrinolytic, has been tested in rabbit models with positive results, suggesting that the PAI-1 resistance and durability of intrapleural scuPA may be advantageous, and may play a substantial role in the future of IPFT. scuPA is currently undergoing a phase 1 dose escalation clinical trial testing in patients with loculated empyema (NIH 1U01HL121841-01A1)

Thoracoscopy

The use of local anaesthetic thoracoscopy, as a combined diagnostic and therapeutic procedure for suspected malignant pleural disease has been well established[89] and is commonly practiced in most specialist centres. There has been an increased interest in its role in the management of pleural infection. In theory, thoracoscopy has the advantage of allowing the chest physician to mechanically divide and break up septations in the pleural space, followed by targeted placement of a chest tube under direct vision for optimal position and drainage, associated with a lavage procedure. The initial data is promising; results from a retrospective series of 127 patients quoted a success rate of 91% with a 6% thoracotomy conversion rate[90]. A separate smaller case series of 41 patients from another group reported similar results [91] and there are currently two randomised control trials recruiting in Europe and the United States comparing this modality to standard of care and IPFT. It is safe to say that this treatment strategy is likely to be limited to centres with significant expertise and on-site access to thoracic surgery, but nonetheless, forms a potentially exciting development as an option for the older, frail patient with higher surgical and general anaesthetic risk.

Surgery

Sir William Osler (1849-1919) once famously quoted that "Empyema needs the cold steel of a surgeon rather than some fool of a physician". Sadly, he went on to die of surgical complications after undergoing surgery.

Current guidelines advocate the use of surgery when an advanced fibrotic state is suspected with extensive pleural thickening that is likely to require decortication, or more commonly, as rescue therapy when patients with empyema or a complex parapneumonic effusion fail medical treatment[41], usually judged 5-7 days into the initiation of treatment[92,93]. Randomised trial data demonstrates that this scenario will occur in 20-30% of cases[21,72]. Failure of medical therapy continues to be defined as clinical evidence of worsening infection or sepsis, combined with residual pleural collection on imaging [41]. Guidelines that made these recommendation were based on low quality evidence. To date, there is no robust data to identify which patients are likely to benefit from surgical intervention, or a means to predicting the optimal point at which they should be referred. The development of clinical risk scores, such as the RAPID score [38], that enable us to prognosticate at the time of presentation, are likely to go some way in achieving this. The adoption of video assisted thoracoscopic surgery (VATS) as the 1st line surgical option in pleural infection [94,95] has meant that this less invasive procedure is available to more patients fit enough to undergo an operation. A meta-analysis comparing VATS to traditional thoracotomy and decortication has demonstrated it's superiority with advantages of VATS including reduced post-op morbidity, complications and length of hospital stay, with similar success rates in terms of resolution of disease [96].

The question remains as to whether VATS at initial presentation is superior to medical treatment. A recent Cochrane review suggested that there is no statistically significant difference in mortality between primary surgical and non surgical management of pleural empyema for all age groups [97]. However, there was insufficient evidence to assess the impact of fibrinolytic therapy. The authors concluded that there was limited evidence to suggest that VATS reduced length of stay in hospital. This would appear to be more consistent with data from the larger randomised studies in children, which have shown no clinical benefit and an increased cost of VATS compared with chest drainage and fibrinolytic therapy[98–101]. Delayed referral as well as pleural infection caused by more resistant gram negative organisms is clearly associated with worse outcomes and increasing rate of conversion of VATS to open thoracotomy [102]. Open window thoracotomy remains a potentially life saving option for patients with pleural space infection after thoracic surgery procedures such as pneumonectomy and lobectomy, and the use of vacuum-associated closure devices might enhance the care of these patients by accelerating recovery [101,103].

CONCLUSION AND FUTURE DIRECTIONS

The use of IPFT has revolutionized the medical management of pleural infection and meant that fewer patients require surgical intervention. However, just as we have seen heterogeneity shape the clinical phenotyping of other respiratory disorders, the same may be applicable to pleural infection. Clinical scoring systems, taking into account clinical, radiological, microbiological as well as biochemical features, may help stratify patients at presentation. A better understanding of the mechanisms of effusion formation and action of fibrinolytic therapy, may help us determine which patients are less likely to respond to IPFT, and therefore benefit from early surgery. Further research is required to optimise the dosing regimen of IPFT, administration protocol, timing of the intervention as well as refining patient selection. This may extend the safety profile and better justify the associated costs. Longer term effects of the IPFT, such as preservation of lung function, remain unknown. Saline irrigation through a chest tube is a relatively simple intervention that may soon enhance standard of care medical treatment. A much larger cohort is needed to better define the optimal drug regimen, route and duration of antimicrobial therapy for empyema, and data on intrapleural antibiotics remains scarce. It has already been proven that the microbiological profile of the pleural space differs from lung parenchymal infections and methods of improving the culture yield, such as parietal pleural biopsy is showing promising results. Medical thoracoscopy in the context of pleural infection may be an early treatment option, with potential diagnostic as well as a therapeutic benefit. Rapid inactivation of IPFT by inhibitors such as PAI-1 in pleural fluid may mean that novel agents such as scuPA could prove advantageous.

REFERENCES

1. Grijalva CG, Zhu Y, Nuorti JP, Griffin MR. Emergence of parapneumonic empyema in the USA. *Thorax*. 2011;66(8):663-668. doi:10.1136/thx.2010.156406

2. Lisboa T, Waterer GW, Lee YCG. Pleural infection: changing bacteriology and its implications. *Respirol Carlton Vic*. 2011;16(4):598-603. doi:10.1111/j.1440-1843.2011.01964.x

3. Piccolo F, Popowicz N, Wong D, Lee YCG. Intrapleural tissue plasminogen activator and deoxyribonuclease therapy for pleural infection. *J Thorac Dis*. 2015;7(6):999-1008. doi:10.3978/j.issn.2072-1439.2015.01.30

4. FRANCE J. *Journal of Medieval Military History: Volume VIII*. NED-New edition. (ROGERS CJ, DeVRIES K, eds.). Boydell and Brewer; 2010. http://www.jstor.org/stable/10.7722/j.ctt7zstnd. Accessed February 21, 2018.

5. Peters RM. Empyema thoracis: historical perspective. *Ann Thorac Surg*. 1989;48(2):306-308.

6. Munnell ER. Thoracic drainage. *Ann Thorac Surg*. 1997;63(5):1497-1502.

7. Meyer JA. Gotthard Bülau and closed water-seal drainage for empyema, 1875-1891. *Ann Thorac Surg*. 1989;48(4):597-599.

8. Howe BE. Evaluation of chest suction with an artificial thorax. *Surg Forum*. 1951:1-7.

9. Monaghan SF, Swan KG. Tube thoracostomy: the struggle to the "standard of care." *Ann Thorac Surg*. 2008;86(6):2019-2022. doi:10.1016/j.athoracsur.2008.08.006

10. Sahn SA. Diagnosis and management of parapneumonic effusions and empyema. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007;45(11):1480-1486. doi:10.1086/522996

11. Bhatnagar R, Maskell NA. Treatment of Complicated Pleural Effusions in 2013. *Clin Chest Med*. 2013;34(1):47-62. doi:10.1016/j.ccm.2012.11.004

12. Farjah F, Symons RG, Krishnadasan B, Wood DE, Flum DR. Management of pleural space infections: A population-based analysis. *J Thorac Cardiovasc Surg*. 2007;133(2):346-351.e1. doi:10.1016/j.jtcvs.2006.09.038

13. Finley C, Clifton J, Fitzgerald JM, Yee J. Empyema: an increasing concern in Canada. *Can Respir J*. 2008;15(2):85-89.

14. Shen H-N, Lu C-L, Li C-Y. Epidemiology of pleural infections in Taiwan from 1997 through 2008: Pleural infections in Taiwan. *Respirology*. 2012;17(7):1086-1093. doi:10.1111/j.1440-1843.2012.02214.x

15. Søgaard M, Nielsen RB, Nørgaard M, Kornum JB, Schønheyder HC, Thomsen RW. Incidence, Length of Stay, and Prognosis of Hospitalized Patients With Pleural Empyema. *Chest*. 2014;145(1):189-192. doi:10.1378/chest.13-1912

16. Bender JM, Ampofo K, Sheng X, Pavia AT, Cannon-Albright L, Byington CL. Parapneumonic Empyema Deaths during Past Century, Utah. *Emerg Infect Dis*. 2009;15(1):44-48. doi:10.3201/eid1501.080618

17. Rahman NM, Kahan BC, Miller RF, Gleeson FV, Nunn AJ, Maskell NA. A Clinical Score (RAPID) to Identify Those at Risk for Poor Outcome at Presentation in Patients With Pleural Infection. *Chest*. 2014;145(4):848-855. doi:10.1378/chest.13-1558

18. Idell S. The pathogenesis of pleural space loculation and fibrosis. *Curr Opin Pulm Med*. 2008;14(4):310-315. doi:10.1097/MCP.0b013e3282fd0d9b

19. Popowicz N, Idell S, Lee YCG. Pathogenesis of pleural infection: A complex warfare: Editorial. *Respirology*. 2018;23(1):8-9. doi:10.1111/resp.13171

20. Lee K-L, Chen W-L, Chen R-J, Lai KS, Chung C-L. Lipoteichoic acid upregulates plasminogen activator inhibitor-1 expression in parapneumonic effusions. *Respirol Carlton Vic*. 2018;23(1):89-95.

21. Rahman NM, Maskell NA, West A, et al. Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection. *N Engl J Med*. 2011;365(6):518-526. doi:10.1056/NEJMoa1012740

22. Lansley SM, Cheah HM, Varano Della Vergiliana JF, Chakera A, Lee YCG. Tissue plasminogen activator potently stimulates pleural effusion via a monocyte chemotactic protein-1-dependent mechanism. *Am J Respir Cell Mol Biol*. 2015;53(1):105-112. doi:10.1165/rcmb.2014-0017OC

23. Wrightson JM, Wray JA, Street TL, et al. Absence of Atypical Pathogens in Pleural Infection. *Chest*. 2015;148(3):e102-e103. doi:10.1378/chest.15-1130

24. Popowicz ND, Lansley SM, Cheah HM, et al. Human pleural fluid is a potent growth medium for Streptococcus pneumoniae. Ho PL, ed. *PLOS ONE*. 2017;12(11):e0188833. doi:10.1371/journal.pone.0188833

25. Lin Y-T, Chen T-L, Siu LK, Hsu S-F, Fung C-P. Clinical and microbiological characteristics of community-acquired thoracic empyema or complicated parapneumonic effusion caused by Klebsiella pneumoniae in Taiwan. *Eur J Clin Microbiol Infect Dis*. 2010;29(8):1003-1010. doi:10.1007/s10096-010-0961-8

26. Chen KY, Hsueh PR, Liaw YS, Yang PC, Luh KT. A 10-year experience with bacteriology of acute thoracic empyema: emphasis on Klebsiella pneumoniae in patients with diabetes mellitus. *Chest*. 2000;117(6):1685-1689.

27. Maskell NA, Batt S, Hedley EL, Davies CWH, Gillespie SH, Davies RJO. The Bacteriology of Pleural Infection by Genetic and Standard Methods and Its Mortality Significance. *Am J Respir Crit Care Med*. 2006;174(7):817-823. doi:10.1164/rccm.200601-074OC

28. Marks DJB, Fisk MD, Koo CY, et al. Thoracic Empyema: A 12-Year Study from a UK Tertiary Cardiothoracic Referral Centre. Wilkinson RJ, ed. *PLoS ONE*. 2012;7(1):e30074. doi:10.1371/journal.pone.0030074

29. Park C-K, Oh H-J, Choi H-Y, et al. Microbiological Characteristics and Predictive Factors for Mortality in Pleural Infection: A Single-Center Cohort Study in Korea. Trottein F, ed. *PLOS ONE*. 2016;11(8):e0161280. doi:10.1371/journal.pone.0161280

30. Lisboa T, Waterer GW, Lee YCG. Pleural infection: Changing bacteriology and its implications: Pleural infection: changing bacteriology. *Respirology*. 2011;16(4):598-603. doi:10.1111/j.1440-1843.2011.01964.x

31. Boyanova L, Vladimir Djambazov, Gergova G, et al. Anaerobic microbiology in 198 cases of pleural empyema: a Bulgarian study. *Anaerobe*. 2004;10(5):261-267. doi:10.1016/j.anaerobe.2004.06.001

32. Asai N, Suematsu H, Hagihara M, et al. The etiology and bacteriology of healthcare-associated empyema are quite different from those of community-acquired empyema. *J Infect Chemother*. 2017;23(10):661-667. doi:10.1016/j.jiac.2017.04.011

33. Psallidas I, Kanellakis N, Bhatnagar R, et al. S24 A phase i feasibility study in establishing the role of ultrasound-guided pleural biopsies in pleural infection (the audio study). In: BMJ Publishing Group Ltd and British Thoracic Society; 2017:A17.2-A18. doi:10.1136/thoraxjnl-2017-210983.30

34. Ko SC, Chen KY, Hsueh PR, Luh KT, Yang PC. Fungal empyema thoracis: an emerging clinical entity. *Chest*. 2000;117(6):1672-1678.

35. El Solh AA, Alhajjhasan A, Ramadan FH, Pineda LA. A comparative study of community- and nursing home-acquired empyema thoracis. *J Am Geriatr Soc*. 2007;55(11):1847-1852. doi:10.1111/j.1532-5415.2007.01392.x

36. Nielsen J, Meyer CN, Rosenlund S. Outcome and clinical characteristics in pleural empyema: a retrospective study. *Scand J Infect Dis*. 2011;43(6-7):430-435. doi:10.3109/00365548.2011.562527

37. Marks DJB, Fisk MD, Koo CY, et al. Thoracic empyema: a 12-year study from a UK tertiary cardiothoracic referral centre. *PloS One*. 2012;7(1):e30074. doi:10.1371/journal.pone.0030074

38. Rahman NM, Kahan BC, Miller RF, Gleeson FV, Nunn AJ, Maskell NA. A clinical score (RAPID) to identify those at risk for poor outcome at presentation in patients with pleural infection. *Chest*. 2014;145(4):848-855. doi:10.1378/chest.13-1558

39. Corcoran JP, Rahman NM. Effusions from infections: Parapneumonic pleural effusion and empyema. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. 3rd ed. Boca Raton, Florida: CRC Press; 2016:295-330.

40. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. *Am J Med*. 1980;69(4):507-512.

41. Davies HE, Davies RJO, Davies CWH. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. *Thorax*. 2010;65(Suppl 2):ii41-ii53. doi:10.1136/thx.2010.137000

42. Havelock T, Teoh R, Laws D, Gleeson F. Pleural procedures and thoracic ultrasound: British Thoracic Society pleural disease guideline 2010. *Thorax*. 2010;65(Suppl 2):i61-i76. doi:10.1136/thx.2010.137026

43. Soni NJ, Franco R, Velez MI, et al. Ultrasound in the Diagnosis & Management of Pleural Effusions. *J Hosp Med*. 2015;10(12):811-816. doi:10.1002/jhm.2434

44. Maskell NA, Gleeson FV, Darby M, Davies RJO. Diagnostically significant variations in pleural fluid pH in loculated parapneumonic effusions. *Chest*. 2004;126(6):2022-2024. doi:10.1378/chest.126.6.2022

45. Pine JR, Hollman JL. Elevated Pleural Fluid pH in Proteus mirabilis Empyema. *CHEST*. 1983;84(1):109-111. doi:10.1378/chest.84.1.109

46. Bowling M, Lenz P, Chatterjee A, Conforti JF, Haponik EF, Robert Chin J. Perception versus Reality: The Measuring of Pleural Fluid pH in the United States. *Respiration*. 2012;83(4):316-322. doi:10.1159/000335134

47. Menzies SM, Rahman NM, Wrightson JM, et al. Blood culture bottle culture of pleural fluid in pleural infection. *Thorax*. 2011;66(8):658-662. doi:10.1136/thx.2010.157842

48. Chelangara DP, Sadakkathulla U, George T. Improvement in culture yield using blood culture bottles in infected pleural fluid. *Eur Respir J*. 2015;46(suppl 59):PA2584. doi:10.1183/13993003.congress-2015.PA2584

49. Vorster MJ, Allwood BW, Diacon AH, Koegelenberg CFN. Tuberculous pleural effusions: advances and controversies. *J Thorac Dis*. 2015;7(6):981-991. doi:10.3978/j.issn.2072-1439.2015.02.18

50. Biswas B, Sharma SK, Negi RS, Gupta N, Jaswal VMS, Niranjan N. Pleural effusion: Role of pleural fluid cytology, adenosine deaminase level, and pleural biopsy in diagnosis. *J Cytol Indian Acad Cytol*. 2016;33(3):159-162. doi:10.4103/0970-9371.188062

51. Rooper LM, Ali SZ, Olson MT. A minimum fluid volume of 75 mL is needed to ensure adequacy in a pleural effusion: a retrospective analysis of 2540 cases. *Cancer Cytopathol*. 2014;122(9):657-665. doi:10.1002/cncy.21452

52. Dixon G, Lama-Lopez A, Bintcliffe OJ, Morley AJ, Hooper CE, Maskell NA. The role of serum procalcitonin in establishing the diagnosis and prognosis of pleural infection. *Respir Res*. 2017;18. doi:10.1186/s12931-017-0501-5

53. Zou M-X, Zhou R-R, Wu W-J, Zhang N-J, Liu W-E, Fan X-G. The use of pleural fluid procalcitonin and C-reactive protein in the diagnosis of parapneumonic pleural effusions: a systemic review and meta-analysis. *Am J Emerg Med*. 2012;30(9):1907-1914. doi:10.1016/j.ajem.2012.04.004

54. Davies HE, Davies RJO, Davies CWH, on behalf of the BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. *Thorax*. 2010;65(Suppl 2):ii41-ii53. doi:10.1136/thx.2010.137000

55. Kearney SE, Davies CW, Davies RJ, Gleeson FV. Computed tomography and ultrasound in parapneumonic effusions and empyema. *Clin Radiol*. 2000;55(7):542-547. doi:10.1053/crad.1999.0480

56. Porcel JM, Pardina M, Alemán C, Pallisa E, Light RW, Bielsa S. Computed tomography scoring system for discriminating between parapneumonic effusions eventually drained and those cured only with antibiotics: CT for parapneumonic effusions. *Respirology*. 2017;22(6):1199-1204. doi:10.1111/resp.13040

57. McLoud TC, Flower CD. Imaging the pleura: sonography, CT, and MR imaging. *Am J Roentgenol*. 1991;156(6):1145-1153. doi:10.2214/ajr.156.6.2028857

58. Maskell NA, Batt S, Hedley EL, Davies CWH, Gillespie SH, Davies RJO. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med*. 2006;174(7):817-823. doi:10.1164/rccm.200601-074OC

59. Ader A, Reimer P, Kam R, et al. Feasibility of irrigation and instillation of antimicrobial or antibiotic solutions in patients with parapneumonic empyema

— A prospective randomized study. *Indian J Thorac Cardiovasc Surg*. 2008;24(3):184-190. doi:10.1007/s12055-008-0039-8

60. Torbic H, Glasser N, Rostas SE, Alquwaizani M, Hacobian G. Intrapleural Antimicrobial Irrigation for Postpneumonectomy Empyema in Patients With Lung Cancer. *J Pharm Pract*. 2015;28(5):469-472. doi:10.1177/0897190014544787

61. Taryle DA, Good JT, Morgan EJ, Reller LB, Sahn SA. Antibiotic concentrations in human parapneumonic effusions. *J Antimicrob Chemother*. 1981;7(2):171-177.

62. Birkenkamp K, O'Horo JC, Kashyap R, et al. Empyema management: A cohort study evaluating antimicrobial therapy. *J Infect*. 2016;72(5):537-543. doi:10.1016/j.jinf.2016.02.009

63. Nwiloh J, Freeman H, McCord C. Malnutrition: an important determinant of fatal outcome in surgically treated pulmonary suppurative disease. *J Natl Med Assoc*. 1989;81(5):525-529.

64. Rahman NM, Maskell NA, Davies CWH, et al. The relationship between chest tube size and clinical outcome in pleural infection. *Chest*. 2010;137(3):536-543. doi:10.1378/chest.09-1044

65. Hallifax RJ, Psallidas I, Rahman NM. Chest Drain Size: the Debate Continues. *Curr Pulmonol Rep*. 2017;6(1):26-29. doi:10.1007/s13665-017-0162-3

66. Patz EF, Goodman PC, Erasmus JJ. Percutaneous drainage of pleural collections. *J Thorac Imaging*. 1998;13(2):83-92.

67. Hooper CE, Edey AJ, Wallis A, et al. Pleural irrigation trial (PIT): a randomised controlled trial of pleural irrigation with normal saline versus standard care in patients with pleural infection. *Eur Respir J*. 2015;46(2):456-463. doi:10.1183/09031936.00147214

68. Davies HE, Rahman NM, Parker RJ, Davies RJO. Use of indwelling pleural catheters for chronic pleural infection. *Chest*. 2008;133(2):546-549. doi:10.1378/chest.07-1742

69. Corcoran JP, Ahmad M, Mukherjee R, Redmond KC. Pleuro-pulmonary complications of rheumatoid arthritis. *Respir Care*. 2014;59(4):e55-59. doi:10.4187/respcare.02597

70. Tillett WS, Sherry S. THE EFFECT IN PATIENTS OF STREPTOCOCCAL FIBRINOLYSIN (STREPTOKINASE) AND STREPTOCOCCAL DESOXYRIBONUCLEASE ON FIBRINOUS, PURULENT, AND SANGUINOUS PLEURAL EXUDATIONS. *J Clin Invest*. 1949;28(1):173-190. doi:10.1172/JCI102046

71. Cameron R, Davies HR. Intra-pleural fibrinolytic therapy versus conservative management in the treatment of parapneumonic effusions and empyema. *Cochrane Database Syst Rev*. 2004;(2):CD002312. doi:10.1002/14651858.CD002312.pub2

72. Maskell NA, Davies CWH, Nunn AJ, et al. U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection. *N Engl J Med*. 2005;352(9):865-874. doi:10.1056/NEJMoa042473

73. Jaffé A, Bush A. Cystic fibrosis: review of the decade. *Monaldi Arch Chest Dis Arch Monaldi Mal Torace*. 2001;56(3):240-247.

74. Light RW, Nguyen T, Mulligan ME, Sasse SA. The In Vitro Efficacy of Varidase Versus Streptokinase or Urokinase for Liquefying Thick Purulent Exudative Material from Loculated Empyema. *Lung*. 2000;178(1):13-18. doi:10.1007/s004080000002

75. Simpson G, Roomes D, Heron M. Effects of streptokinase and deoxyribonuclease on viscosity of human surgical and empyema pus. *Chest*. 2000;117(6):1728-1733.

76. Thommi G, Shehan JC, Robison KL, Christensen M, Backemeyer LA, McLeay MT. A double blind randomized cross over trial comparing rate of decortication and efficacy of intrapleural instillation of alteplase vs placebo in patients with empyemas and complicated parapneumonic effusions. *Respir Med*. 2012;106(5):716-723. doi:10.1016/j.rmed.2012.02.005

77. Talib SH, Verma GR, Arshad M, Tayade BO, Rafeeque A. Utility of intrapleural streptokinase in management of chronic empyemas. *J Assoc Physicians India*. 2003;51:464-468.

78. Misthos P, Sepsas E, Konstantinou M, Athanassiadi K, Skottis I, Lioulias A. Early use of intrapleural fibrinolytics in the management of postpneumonic empyema. A prospective study. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. 2005;28(4):599-603. doi:10.1016/j.ejcts.2005.07.005

79. Diacon AH, Theron J, Schuurmans MM, Van de Wal BW, Bolliger CT. Intrapleural streptokinase for empyema and complicated parapneumonic effusions. *Am J Respir Crit Care Med*. 2004;170(1):49-53. doi:10.1164/rccm.200312-1740OC

80. Chin NK, Lim TK. Controlled trial of intrapleural streptokinase in the treatment of pleural empyema and complicated parapneumonic effusions. *Chest*. 1997;111(2):275-279.

81. Willsie-Ediger SK, Salzman G, Reisz G, Foreman MG. Use of intrapleural streptokinase in the treatment of thoracic empyema. *Am J Med Sci*. 1990;300(5):296-300.

82. Gervais DA, Levis DA, Hahn PF, Uppot RN, Arellano RS, Mueller PR. Adjunctive intrapleural tissue plasminogen activator administered via chest tubes placed with imaging guidance: effectiveness and risk for hemorrhage. *Radiology*. 2008;246(3):956-963. doi:10.1148/radiol.2463070235

83. Popowicz N, Bintcliffe O, De Fonseka D, et al. Dose De-escalation of Intrapleural Tissue Plasminogen Activator Therapy for Pleural Infection. The Alteplase Dose Assessment for Pleural Infection Therapy Project. *Ann Am Thorac Soc*. 2017;14(6):929-936. doi:10.1513/AnnalsATS.201609-673OC

84. Kheir F, Cheng G, Rivera E, et al. Concurrent Versus Sequential Intrapleural Instillation of Tissue Plasminogen Activator and Deoxyribonuclease for Pleural Infection. *J Bronchol Interv Pulmonol*. January 2018. doi:10.1097/LBR.0000000000000461

85. Mehta HJ, Biswas A, Penley AM, Cope J, Barnes M, Jantz MA. Management of Intrapleural Sepsis with Once Daily Use of Tissue Plasminogen Activator and Deoxyribonuclease. *Respiration*. 2016;91(2):101-106. doi:10.1159/000443334

86. Lee YCG, Idell S, Stathopoulos GT. Translational Research in Pleural Infection and Beyond. *Chest*. 2016;150(6):1361-1370. doi:10.1016/j.chest.2016.07.030

87. Chung C-L, Chen C-H, Sheu J-R, Chen Y-C, Chang S-C. Proinflammatory cytokines, transforming growth factor-beta1, and fibrinolytic enzymes in loculated and free-flowing pleural exudates. *Chest*. 2005;128(2):690-697. doi:10.1378/chest.128.2.690

88. Florova G, Azghani A, Karandashova S, et al. Targeting of plasminogen activator inhibitor 1 improves fibrinolytic therapy for tetracycline-induced pleural injury in rabbits. *Am J Respir Cell Mol Biol*. 2015;52(4):429-437. doi:10.1165/rcmb.2014-0168OC

89. Rahman NM, Ali NJ, Brown G, et al. Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. 2010;65 Suppl 2:ii54-60. doi:10.1136/thx.2010.137018

90. Brutsche MH, Tassi G-F, Györik S, et al. Treatment of sonographically stratified multiloculated thoracic empyema by medical thoracoscopy. *Chest*. 2005;128(5):3303-3309. doi:10.1378/chest.128.5.3303

91. Ravaglia C, Gurioli C, Tomassetti S, et al. Is medical thoracoscopy efficient in the management of multiloculated and organized thoracic empyema? *Respir Int Rev Thorac Dis*. 2012;84(3):219-224. doi:10.1159/000339414

92. Mavroudis C, Symmonds JB, Minagi H, Thomas AN. Improved survival in management of empyema thoracis. *J Thorac Cardiovasc Surg*. 1981;82(1):49-57.

93. Pothula V, Krellenstein DJ. Early aggressive surgical management of parapneumonic empyemas. *Chest*. 1994;105(3):832-836.

94. Hajjar WM, Ahmed I, Al-Nassar SA, et al. Video-assisted thoracoscopic decortication for the management of late stage pleural empyema, is it feasible? *Ann Thorac Med*. 2016;11(1):71-78. doi:10.4103/1817-1737.165293

95. Scarci M, Abah U, Solli P, et al. EACTS expert consensus statement for surgical management of pleural empyema. *Eur J Cardiothorac Surg*. 2015;48(5):642-653. doi:10.1093/ejcts/ezv272

96. Chambers A, Routledge T, Dunning J, Scarci M. Is video-assisted thoracoscopic surgical decortication superior to open surgery in the management of adults with primary empyema? *Interact Cardiovasc Thorac Surg*. 2010;11(2):171-177. doi:10.1510/icvts.2010.240408

97. Redden MD, Chin TY, van Driel ML. Surgical versus non-surgical management for pleural empyema. *Cochrane Database Syst Rev*. 2017;3:CD010651. doi:10.1002/14651858.CD010651.pub2

98. Sonnappa S, Cohen G, Owens CM, et al. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. *Am J Respir Crit Care Med*. 2006;174(2):221-227. doi:10.1164/rccm.200601-027OC

99. Marhuenda C, Barceló C, Fuentes I, et al. Urokinase versus VATS for treatment of empyema: a randomized multicenter clinical trial. *Pediatrics*. 2014;134(5):e1301-1307. doi:10.1542/peds.2013-3935

100. St Peter SD, Tsao K, Spilde TL, et al. Thoracoscopic decortication vs tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial. *J Pediatr Surg*. 2009;44(1):106-111; discussion 111. doi:10.1016/j.jpedsurg.2008.10.018

101. Corcoran JP, Wrightson JM, Belcher E, DeCamp MM, Feller-Kopman D, Rahman NM. Pleural infection: past, present, and future directions. *Lancet Respir Med*. 2015;3(7):563-577. doi:10.1016/S2213-2600(15)00185-X

102. Lardinois D, Gock M, Pezzetta E, et al. Delayed referral and gram-negative organisms increase the conversion thoracotomy rate in patients undergoing video-assisted thoracoscopic surgery for empyema. *Ann Thorac Surg*. 2005;79(6):1851-1856. doi:10.1016/j.athoracsur.2004.12.031

103. Palmen M, van Breugel HNAM, Geskes GG, et al. Open window thoracostomy treatment of empyema is accelerated by vacuum-assisted closure. *Ann Thorac Surg*. 2009;88(4):1131-1136. doi:10.1016/j.athoracsur.2009.06.030

Figure legends

Figure 1: Chest X-ray shows the partial encystment of the pleural collection as noted by the steep upper border of the opacity

Figure 2: A Chest X-ray shows a rounded opacity that does not obscure the heart borders or the diaphragm. B Chest CT reveals posteriorly loculated pleural collection. Note the enhancing pleura (split pleura sign) and the extralpeural fat hypertrophy

Figure 3: Ultrasound images of A) heavily septated pleural effusion and B) echogenic free pleural effusion