Current medical management of pleural infection

Pleural infection develops in approximately 65,000 patients each year in the USA and the UK. Parapneumonic pleural effusions (PPEs) and pleural empyema (PE) represent a frequently difficult diagnostic and therapeutic challenge in clinical practice due to their heterogeneity. Over the past decade, their devastating incidence and clinical seriousness have stimulated innumerable research studies, with any possible therapeutic approach. However, there are still many uncertainties concerning the diagnosis and treatment of PPE and PE. Most of these studies have been undertaken due to the attention currently being directed at the practice of evidence-based medicine with interventions that are supported by large, randomized controlled studies. Furthermore, pressures on physicians to discharge patients from the hospital in record time, while decreasing morbidity and patient-related charges, are forcing the re-evaluation of current practices, many of which are based on anecdote or experience. Additionally, a lack of controlled studies concerning the management of PPE and PE was noted in recent guidelines [1-3]. This lack of evidence originates partly from hardships that are inherent in the investigation of pleural infections, which represent heterogeneous disorders with outcomes strongly influenced by multiple factors such as coexisting diseases, underlying lung function, severity of associated pneumonia, extent of pleural inflammation and virulence of causative pathogens.

It is estimated that at least 40% of patients with pneumonia develop an effusion [1]. Delays in diagnosis and treatment are common and may contribute to increased morbidity and mortality. There is considerable variation in the aggressiveness and course of parapneumonic effusions. Therefore, the spectrum of appropriate therapy may vary from a conservative approach in uncomplicated effusions, to tube drainage with or without fibrinolytic therapy in complicated effusions to aggressive surgical intervention in severe multiloculated empyemas.

Under appropriate conditions, the use of fibrinolytics intrapleurally appears to enhance intercostal tube drainage, reducing the requirement for subsequent surgical mechanical debridement. It should be noted that it still remains to be proven whether the increase in pleural fluid drainage has any measurable impact on outcome. Recently, there has been interest in other intrapleural agents, including combination drugs consisting of streptokinase, streptodornase-α and DNase.

This review discusses the current diagnostic and therapeutic options, and also presents some of the future perspectives in the medical management minefield of parapneumonic effusions and empyemas. Surgical treatment modalities represent the issue of another review article and thus have been excluded from our data.
Definitions
A PPE is an accumulation of exudative pleural effusion associated with bacterial pneumonia, lung abscess or bronchiectasis [1–3]. An effusion is referred to as an empyema when the concentration of leukocytes becomes macroscopically evident as a thick, highly viscous, whitish-yellow, opaque and turbid fluid (pus). Other common causes include surgical procedures, traumas and esophageal perforation. The empyema consists of fibrin, cellular debris and living or dead bacteria. There is no consensus on the number of white blood cell (WBC) counts, or the biochemistry for an empyema. The extent of the definition of empyema in a nonpurulent fluid with only the presence of a positive Gram stain or culture is not widely accepted [4].

Uncomplicated (simple) PPEs are usually small, not loculated and not infected. Most often, they resolve spontaneously under antibiotic treatment. Complicated PPEs are usually associated with pleural invasion of the infectious agent and require tube thoracostomy and possibly further interventions. A loculated PPE is a nonfree-flowing pleural effusion. A multiloculated PPE is a pleural effusion with more than one loculus [1–5].

Pathophysiology
The evolution of a simple PPE to an empyema represents a continuous progression from a small amount of free-flowing, noninfected, nonpurulent pleural fluid to a large amount of frank pus which is multiloculated and associated with thick visceral pleura that prevents the underlying lung from expanding if the fluid is removed. Pleural infection may also develop without evidence of pneumonia – also known as primary empyema.

When a patient develops pneumonia, the pleura responds to the presence of microbes with a vigorous inflammatory response. The rate of pleural fluid formation, consisting of an exudate of WBC and proteins, is increased. The increase is mainly due to lung interstitial fluid and secondary to increased permeability of the capillaries in the pleurae. When the amount of fluid entering the pleural space exceeds the capacity of the lymphatics to reabsorb the fluid, a pleural effusion develops. Initially, the pleural fluid has normal glucose, pH and the lactic acid dehydrogenase (LDH) levels and the WBC count are low [5]. Mesothelial cells are actively phagocytic, initiating an inflammatory response when activated by the presence of bacteria, by releasing a battery of chemokines (C-X-C group), cytokines (interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor [TNF]-α), oxidants and proteases [6].

The formation of parapneumonic effusions can be divided into four stages [7,8]:

- The pleuritis sicca stage: the inflammatory process extends to the visceral pleura, causing a local reaction. This leads to an audible pleural rub and pleuritic chest pain originating from the sensitive innervation of the adjacent parietal pleura. Numerous patients with pneumonia report pleuritic pain without developing a pleural effusion indicating that the involvement of the pleura may be limited to this stage.

- The exudative stage: is characterized by a small, sterile, neutrophil predominant exudate, secondary to increased permeability of the visceral pleura. The following accumulation of fluid in the pleural space is probably the combined result of the influx of pulmonary interstitial fluid and a local microvascular exudate. Pleural fluid has high protein levels, normal glucose, pH and LDH; however, it is not infected. The process is reversible with the institution of appropriate antibiotic therapy during the early exudative phase.

- The fibropurulent stage: if pneumonia progresses, bacteria continue to multiply in the lung with invasion and persistence in the pleural space, while endothelial injury becomes more prominent with increased pleural fluid formation. Pleural fluid biochemical parameters change dramatically, mirroring elevated metabolic activity and cell death in leukocytes and bacteria. The latter results in decreased glucose and pH whereas LDH rises within pleural fluid. Pleural fluid becomes clottable, as fibrin and collagen are deposited in a continuous sheet covering the visceral and parietal pleura, compartmentalizing the pleural fluid into loculations. The pleural fluid volume may increase further due to blockage of the parietal pleura stoma by fibrin and collagen and mesothelial cells. Early in this stage, antibiotics alone may be effective; however, in the later stages pleural-space drainage is needed.

- The organization/empyema stage: if empyema fails to resolve on treatment, the organizational stage is entered, in which thick rinds of fibrous tissue are deposited within the hemithorax forming a single or multiple loculations. The organization stage occurs with
the growth of fibroblasts into the exudates, to form an inelastic pleural peel and dense fibrous septations. Empyema fluid is a thick, purulent coagulum which may not be adequately drained by tube thoracostomy. Empyema, with the formation of frank pus, may arise from a parapneumonic effusion. However, 25% of empyemas occur after trauma or surgery [8]. The rapidity and extent of this process are affected by the type and virulence of the organism [9]. Untreated empyema rarely resolves spontaneously. Patients with empyema always require drainage for resolution of pleural sepsis.

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**Classification of parapneumonic pleural effusions & empyema**

Innumerable classification schemes have been suggested to classify the broad spectrum of PPEs. A common classification divides PPEs into three categories, namely uncomplicated and complicated PPE and thoracic empyema, corresponding to the aforementioned stages of PPE. The American College of Chest Physicians has recently developed a new classification of PPE and empyema which is based upon the radiologic characteristics of the effusion, the pleural fluid bacteriology and the pleural fluid chemistry (Box 1). The key aspects to note concerning this classification are the characteristics indicating that the patient has a moderate-to-high risk of a poor outcome without drainage. Radiologic characteristics associated with a poor prognosis include an effusion that occupies more than 50% of the hemithorax, is loculated, or is associated with thickened parietal pleura. The pleural fluid radiologic, bacteriologic and chemistry prognosticators associated with a poor outcome in patients with complicated PPE are also shown in Box 1 [10]. Several pleural fluid parameters have been described to assess the severity and predict the clinical course of PPE. Patients with complicated PPE tend to have a lower pleural fluid pH and glucose level and a higher LDH activity. The superiority of the pH over glucose or LDH measurements in PPE/PE has been confirmed in a meta-analysis of seven studies [10]. The decision threshold to identify complicated effusions and consequently to assess disease prognosis, ranged between pH 7.21 and 7.29. Moreover, there is a general consensus that pleural fluid pH is the most important chemical parameter to predict the further course of a PPE/PE and various recommendations have been made as to the best cut-off point to distinguish complicated from uncomplicated cases [1,2,10]. However, it should be kept in mind that pleural fluid pH may not be useful in patients with systemic pH alterations and in infections due to *Proteus* species, which induce a local metabolic alkalosis due to ammonia production. It is also possible to find pleural fluid pH with different macroscopic characteristics and pH values in loculated pleural effusions [1–3].

**Epidemiology & bacteriology**

Pleural infection caused by underlying pneumonia is the most common cause of empyema, accounting for 70% of reported cases. Pleural empyemas occur in 5 to 10% of patients with PPE and appear to affect the elderly and debilitated more frequently, as well as men more than women, and hospitalized patients with community-acquired pneumonia. Risk factors for their development include comorbidities such as diabetes mellitus, alcohol abuse, gastroesophageal reflux, rheumatoid arthritis, chronic lung disease and intravenous drug abuse [1,3]. Clinical factors that predict the presence of anaerobic pneumonia include poor dental hygiene, sedative drug use, alcoholism, seizures and mental retardation [3]. Empyema may develop as a complication of pneumonia, or may follow surgery, trauma or iatrogenic procedures [3,4]. It may also occur as a ‘primary infection’ without evidence of parenchymal lung infection. Rare causes of empyema include postobstructive pneumonia due to foreign body aspiration or tumor [1,3].

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**Box 1. Indicators of a poor prognosis with complicated parapneumonic effusions.**

- Fluid is pus.
- Positive Gram stain or culture.
- Pleural fluid pH of less than 7.20.
- Pleural fluid glucose less than 60 mg/dl.
- Pleural fluid lactic acid dehydrogenase over three times the upper limit of normal for serum.
- Loculated pleural fluid.
The role of the pathogen in the underlying pneumonia and the likelihood of the patient developing PPE are not clear, since there are no comparative studies from a single institution. The bacteriology of empyema is extremely varied and there are significant differences between organisms responsible for community- and hospital-acquired infection. Before the advent of modern antibiotics the most common causes of community-acquired pleural infection were streptococcal (*Streptococcus milleri* and *Streptococcus pneumoniae*) and staphylococcal species. The current series of empyemas support the continuing role of these organisms while documenting the emergence of anaerobes and Gram-negative organisms as common pathogens. Conversely, cases of hospital-acquired infection are most commonly caused by methicillin-resistant *Staphylococcus aureus* (MRSA), other *Staphylococci* and *Enterobacteria* [3,4].

**Diagnosis & investigations**

Physicians should be alert for PPE in any patient with pulmonary infection who has a pleural effusion at presentation. The clinical presentation of patients with PPE includes fever, pleurodynia, cough and dyspnea. However, up to 10% of patients with PPE and empyema are relatively asymptomatic, whereas 60 to 80% have underlying comorbidities. Diagnostic thoracentesis is recommended before the administration of antibiotics to improve the diagnostic yield of pleural fluid culture. Current guidelines advise that pleural fluid should be sampled in every patient where pleural infection is considered a possibility, except in very small effusions (<10 mm) which can only be observed [11]. The presence of frank pus at thoracentesis is diagnostic of empyema, regardless of other tests. A foul-smelling pleural fluid suggests the presence of anaerobic bacteria [3].

**Pleural fluid cytology**

PPE/PE are polymorphonuclear-dominated effusions. The absence of which suggests an alternative diagnosis (i.e., predominance of lymphocytes in an exudate is most often associated with tuberculosis or malignancy). The discovery of food particles in the pleural fluid suggests the presence of an esophageal–pleural fistula [3].

**Radiology**

Radiology is pivotal in the evaluation and appropriate management of PPE. A chest radiograph showing a pleural-based opacity that has an abnormal contour or does not flow freely on lateral decubitus views, confirms the presence of pleural fluid, which in the setting of pleural infection is often loculated with multiple air-fluid levels. The lateral decubitus film can detect pleural effusion as small as 5 ml and is used in the diagnosis of a thoracentesis. However, the widespread availability of thoracic ultrasonography has largely superseded the latter technique. Ultrasonography allows precise assessment of loculations and is the method of choice to guide thoracentesis or place a chest tube (Figure 1). Furthermore, it can detect small amounts of pleural fluid and reliably distinguishes small effusions from pleural thickening [3]. Moreover, ultrasonography is associated with a low complication rate and has a success rate in attempted fluid aspiration approaching 100%.
Although diagnosis can be facilitated by thoracentesis under ultrasonography guidance, optimal management requires a chest CT scans with contrast, which enhances the pleural surface and assists in delineating pleural fluid loculi [13]. A CT scan can show pleural abnormalities at an earlier stage than other modalities. It is useful in distinguishing pleural from parenchymal abnormalities and lung abscesses from empyema. Moreover, it is valuable in determining the precise location and extent of pleural disease. Finally, magnetic resonance imaging (MRI) may be useful in identifying loculated collections and chest wall involvement. Nevertheless, its use in the clinical evaluation of pleural infection is limited.

Methods for treatment of PPE/PE

The benefit of draining large pleural effusions and empyemas has been recognized since the time of Hippocrates. Nonetheless it is widely acceptable that the presence of loculations may impede the free drainage of effusions and prevent lung re-expansion. Currently there are several medical therapeutic choices for the modern treatment of the PPE/PE (Box 2). Nonsurgical treatment options to reduce the impact of adhesions and locule, in addition to appropriate antibiotic therapy, include single and multiple thoracentesis and/or single and multiple intercostal tube thoracostomies with or without intrapleural fibrinolytic agents. Surgical options include direct-vision and video-assisted thoracoscopic surgical adhesolysis, limited and full thoracotomy with adhesolysis and possible decortication for severe pleural thickening. Authors have focused on the current level of knowledge regarding medical management of PPEs and PEs and conducted a systematic review of the literature concerning its efficacy and safety. Surgical therapeutic modalities were excluded from our data since they represent the focus of another review article and should be analyzed separately.

Antibiotic therapy

Antibiotic therapy is indicated for all patients with PPE or PE. Early institution of appropriate antibiotic therapy may minimize the development of PPE and eradicate small effusions before they develop into complicated PPE and PE. The
choice of antibiotic should be based on the results of blood and pleural fluid cultures and sensitivities, depending primarily on whether the pneumonia is community or hospital acquired. Nonetheless, it is worth mentioning that cultures are positive in less than 30% of cases, complicating the early institution of the appropriate regimen. Thus, initial treatment should follow the existing guidelines for treatment of community- or hospital-acquired pneumonia [13]; however, with the following in mind: antibiotics that exhibit satisfactory penetration into the pleural fluid include the penicillins, cephalosporins, aztreonam, clindamycin and ciprofloxacin [14]. Community-acquired pneumonia requires antibiotic cover for community pathogens and anaerobes; choices include a second-generation cephalosporin or intravenous aminopenicillin, plus therapy for anaerobic infection (clindamycin). In hospital-acquired empyema, treatment for both Gram positive and Gram negative aerobic organisms as well as anaerobes is needed and additionally highly resistant bacteria should be considered. Options include antipseudomonal quinolones (carbapenems), antipseudomonal penicillins, third-generation cephalosporins or even vancomycin for MRSA species. A change to oral antibiotics may be considered following clinical improvement and resolution of fever. The optimal duration of antibiotic treatment is unclear, although it is likely to be at least 3 weeks [15]. However, there is still debate over the use of intrapleural antibiotics. Several studies have stated positive results but none of them included a randomized control group [15].

Nutritional support
Malnutrition is common in cases of empyema. The availability of nutritional support represents a crucial aspect of the management of the underlying lung disease. Adequate nutrition with additional support is likely to be beneficial for patients with empyema since many require supplementary nasogastric feeding and parenteral nutrition [2].
the β-hemolytic streptococci (exotoxin), which indirectly activates the fibrinolytic system. Urokinase is a direct plasminogen activator, isolated initially from human urine. For each molecule of urokinase, one molecule of plasmin is produced, thus making more efficient use of the preexisting plasminogen.

Clinical trials of intrapleural fibrinolytics

Intrapleural instillation of fibrinolytic agents (usually streptokinase or urokinase) has been shown, in a number of small studies, to be an effective and safe mode of treatment in complicated PPE and PE, minimizing the need for surgical intervention. However, the latter statement should be treated with caution since these studies have not addressed this outcome adequately and therefore it could be misleading.

The mean success rate in the published uncontrolled series of streptokinase is approximately 82% (range: 44–100%) and that of urokinase is 84% (55–100%) [36,37,40–51]. To date, six controlled and/or randomized trials of intrapleural fibrinolytics have been reported. Bouros and colleagues performed a double-blind, randomized, controlled trial comparing streptokinase 250,000 µl versus urokinase 100,000 µl and ultimately suggested that streptokinase and urokinase could be used with equivalent efficacy and safety [36]. The first randomized, double-blind placebo-controlled trial was reported by Davies and colleagues in 24 patients with pleural infection. Patients were randomized to receive either streptokinase or saline placebo [37]. Clinical end points did not show a significant difference between the intervention and control groups. In addition, Bouros and colleagues compared urokinase and saline placebo in 31 patients with pleural infection, in a double-blind, parallel study which showed successful pleural drainage was significantly more frequent in those receiving urokinase [52]. However, the study was not large enough to address issues such as mortality, surgery rate or safety.

The fourth randomized, controlled study was conducted by Tuncozgur and colleagues [53]. Patients were randomized for treatment with either urokinase or normal saline. The authors concluded that urokinase provides a better outcome and reduces the need for decortication. The next placebo-controlled trial was reported last year. The study by Diacon and colleagues [42] was an important addition as the first randomized placebo-controlled trial of intrapleural streptokinase that employed pragmatic clinical outcomes (need of surgery or death) as primary end points [42,55]. Streptokinase-treated patients presented with a higher clinical success rate and fewer referrals for surgery. The authors stated that intrapleural streptokinase adjunctive to chest tube drainage reduces the need for surgery and improves the clinical treatment success in patients with PE.

Due to the limited number of patients enrolled in the aforementioned studies, a recent meta-analysis from the Cochrane library concluded on the basis of the above observation, that while fibrinolytics reduced hospital stay and time-to-defervescence and offered some benefit in terms of radiographic improvement and treatment failure, the evidence was not consistent and given the small sample size, the benefit of fibrinolytics remained unproven. The authors stated that results from this meta-analysis are valid only when data from all studies are pooled, evidence that renders major uncertainty on the reliability and scientific rigidity of this observation given the heterogeneity and diversity of the studied conditions and populations. Ultimately, they highlight the need for further randomized controlled trials in a considerable number of patients to safely recommend intrapleural fibrinolysis as an important adjunctive treatment to intercostal tube drainage.

With this aim in mind, the Multicenter Intrapleural Sepsis Trial (MIST) was recently conducted by Maskell and colleagues [43]. This double-blind trial is the largest randomized study of fibrinolytics and included 454 patients with pleural infection. Patients were randomly assigned to receive either intrapleural streptokinase or placebo twice daily for 3 days. There was no difference in mortality or rates of surgery (primary end points). Furthermore, no statistical significant difference was notable between the streptokinase and placebo groups in terms of radiographic outcome, length of hospital stay and improvement in lung function several months after discharge. Therefore, the largest randomized trial states no beneficial effect of the application of fibrinolytics in the treatment of pleural infection. Nonetheless, a critical review of the trial suggests that the largest weakness was the late use of streptokinase in the clinical course, with median time from first symptom to randomization of approximately 2 weeks. Furthermore, for chest tube insertion and follow-up no image guidance was used, the experience was probably not the same through all centers and the catheters used were a small bore to drain...
cases with empyema. Nevertheless, these results and the conclusion of the meta-analysis described above, underscore the point that any value of intrapleural fibrinolysis remains largely unproven at the present time. Taking into account these limitations, until new well defined, randomized, controlled trials evaluating the validity of fibrinolytic therapy in loculated PPE are available, our view is that they can be used by experienced physicians using the appropriate sized image-guided catheters, avoiding cases of PE [54–56].

Side effects, contraindications, regimens & efficacy

Most reported side effects due to intrapleural fibrinolytic agents are immunologic and occur with intrapleural streptokinase. The initial use of nonpurified solutions of streptokinase resulted in frequent febrile reactions, general malaise and leukocytosis. Newer preparations cause far fewer allergic reactions, ranging from 0 to 20% for fever [18–20]. Evidence for local and systemic hemorrhage is scarce [35]. Systemically administered streptokinase generates an antibody response that can neutralize later administration of streptokinase [57–64]. Urokinase is nonantigenic but may still cause acute reactions (due to immediate hypersensitivity and histamine release) with fever [65] and cardiac arrhythmia [66]. A case of acute hypoxemic respiratory failure following intrapleural instillation of both streptokinase and urokinase for empyema drainage has also been reported [67].

Contraindications for intrapleural administration of fibrinolytics are still elusive. However, a thorough review of the literature revealed absolute and relative contraindications (Box 3) [18].

Fibrinolytic regimens include streptokinase 250,000 IU daily, or 250,000 IU over 12 h, or urokinase 100,000 IU daily retained for 2 to 4 h in the pleural space are the recommended regimens [2]. The effective half-life of both fibrinolytics is less than 30 min and it is plausible that fibrin deposition occurs during the period between doses [69,70]. It may therefore be appropriate to administer more frequently than daily [44].

Early administration of fibrinolytic agents before significant collagen is deposited in the pleural space dramatically increases their effectiveness [55,56]. Measurement of pleural fluid drainage, laboratory findings (WBC count) and radiographic results are used to monitor treatment efficacy [21]. The criteria for abandoning conservative therapy with fibrinolytics and adopting a surgical approach are still ambiguous. In the case of fever persistence, signs of pleural sepsis, markedly elevated WBC count with an elevated proportion of polymorphonuclear cells, or inadequate drainage after three to five instillations, the clinician should reevaluate whether or not alternative therapy should be employed. In this situation, further invasive intervention, such as thoracoscopy is recommended [70].

Other agents

Over the last few years, an emerging interest regarding the application of streptodornase, the coagent originally used has occurred [5]. As an adjuvant or single fibrinolytic agent, it has been shown to liquify pus more effectively in vitro than streptokinase [71,72]. In vivo case reports and series are sparse [70,71]. Tillett’s original empirical dose of streptodornase was 60,000 units/instillation, with the more recent literature suggesting 25 to 50,000 units. One case study used 23 doses of streptokinase 100,000 units/streptodornase 25,000 units without side effect [16]. Larger trials are needed to demonstrate the benefit and safety of streptodornase.

Recent studies indicate the usefulness of a tissue-plasminogen activator (t-PA, Alteplase) as a therapeutic agent for PPE/PE. A downregulation of endogenous t-PA in pleural fluid or inhibition of plasminogen and plasmin by plasminogen activator inhibitors-1 and -2 and other mediators [66,75,76], could support the pathogenesis of fibrin deposition in exudative pleural effusions. However, there are only a few case reports and a retrospective study in pediatric patients documenting promising results [76–78]. These data underline the necessity for randomized controlled trials to be conducted in order to shed further light into the efficacy, dosing and safety of intrapleural alteplase in the treatment of

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**Box 3. Absolute and relative contraindications of fibrinolytic treatment.**

**Absolute**
- History of allergic reaction to the agent.
- Bronchopleural fistula.
- Trauma or surgery within 48 h.

**Relative**
- Major thoracic or abdominal surgery within 7 to 14 days.
- History of hemorrhagic stroke.
- Cranial surgery or trauma within 14 days.
- Coagulation defects.
- Previous streptokinase thrombolysis (for streptokinase only).
- Streptococcal infection (for streptokinase only).
patients with CPE and PE [79,80]. In line with this, an ongoing trial by this authors’ study group estimating the efficacy of alteplase in PPE/PE will address the latter important issues.

Empyema pus has a very high content of DNA. Investigators have postulated that DNase is effective in reducing the pus viscosity, and thus improving drainage [81]. Commercially available human recombinant (hr)DNase digests DNA by depolymerization of polymerized deoxyribonucleoproteins of bacteria and may potentially decrease the viscosity of PE pus without the risk of allergic reactions that occur with streptococcal extracts. Simpson and colleagues used an in vitro assay to determine the relative effects of streptokinase versus hrDNase on the viscosity of pus from patients with soft tissue abscesses and PE and documented a beneficial effect of hrDNase in comparison with streptokinase [82,83].

**Medical thoracoscopy (pleuroscopy)**

Thoracoscopy was introduced by Jacobaeus in 1910, primarily as a diagnostic procedure in two cases of exudative (tuberculous) pleuritis. Thoracoscopy was rediscovered by thoracic surgeons at the beginning of this decade and termed surgical thoracoscopy, which is more precisely known as video-assisted thoracoscopic surgery (VATS) [84]. VATS may be more effective than chest tube drainage and less invasive than open thoracotomy for the lung complication, pleural empyema. Conversely, medical thoracoscopy or pleuroscopy when compared with VATS, has the advantage that it can be performed under local anesthesia or conscious sedation in an endoscopy suite using nondisposable rigid instruments. This technique plays a bridging role between medical and surgical management and has assumed a great importance over the last decade. It is considerably less invasive and expensive. Today, the leading diagnostic indication for medical thoracoscopy is an exudative pleural effusion of unknown origin offering a yield of more than 90% in malignancy or tuberculous pleurisy. The effectiveness of this modern and minimally invasive technique in comparison with VATS in the treatment of PPE and/or PE has not yet been clearly determined [85].

**Expert commentary & outlook**

Despite the widespread availability of numerous medical treatment strategies, pleural infection is still associated with a high mortality and morbidity. Factors that should be included in the clinician’s ‘wish list’ are early etiologic diagnosis based on clinical, radiologic and pleural fluid findings and prompt institution of the appropriate treatment. Antibiotic therapy is indicated for all patients with PPE or PE. Early institution of appropriate antibiotic therapy may minimize the development of PPE and eradicate small effusions before they develop into complicated PPE and PE. Once pleural infection is diagnosed, intercostal drainage should be applied, although there is no therapeutic effect after the development of multiloculated effusions. Regarding fibrinolytic agents, their validity has to be re-evaluated in the context of large prospective, contemporaneous studies.

**Highlights**

- Early etiologic diagnosis of pleural infection based on clinical, radiological and pleural fluid findings represents the cornerstone of the appropriate medical treatment.
- Antibiotic therapy is indicated for all patients with parapneumonic pleural effusions (PPEs) or pleural empyema (PEs). Early institution may minimize the development of PPE and eradicate small effusions before they develop into complicated PPE and PE.
- Indications for chest tube drainage are the diagnosis of empyema, the identification of organisms on pleural fluid Gram stain or culture and a pleural fluid pH < 7.20. It may also be used for symptomatic (dyspnea) relief in very large pleural effusions.
- Intrapleural instillation of fibrinolytic agents has been shown, in a number of ‘small’ studies, to be an effective and safe mode of treatment in complicated PPE and PE, minimizing the need for surgical intervention. However, based on the findings of the largest randomized controlled study, their benefit and efficacy still remain unproven. Their validity has to be re-evaluated in the context of large prospective well-defined studies.
- Medical thoracoscopy represents a novel and promising application in the field of medical management of PPE/PE, since it combines video-assisted thoracoscopic surgery efficacy with less side effects and cost. However, effectiveness of this modern and minimally invasive technique in comparison with VATS in the treatment of PPE and/or PE has not yet been clearly determined.
- The role of newer fibrinolytics, like tissue-plasminogen activator and human recombinant deoxyribonuclease, should also be investigated in PPE.
well-defined studies since the limited number of patients included in the above trials combined with the recent results by Maskell and colleagues, pose major limitations and render uncertainty on their applicability and efficacy. Until larger prospective studies capable of accurately assessing whether the benefits of fibrinolytic therapy translate into a reduction in mortality, our current view is to limit their use in centers where VATS is not available or in patients not capable of surgical management.

A comparative study of intrapleural fibrinolytics versus medical thoracoscopic in complicated and loculated PPE is about to start in Europe. The role of newer fibrinolytics, such as t-PA and hrDNase, should also be investigated in PPE.

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Bibliography

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