Parapneumonic pleural effusions and empyema in adults: current practice

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Abstract

About 20% of hospitalized patients with bacterial pneumonia have an accompanying pleural effusion. Parapneumonic effusions (PPE) are associated with a considerable morbidity and mortality. The main decision in managing a patient with a PPE is whether to insert a chest tube (complicated PPE). Imaging (i.e., chest radiograph, ultrasound and computed tomography) and pleural fluid analysis (i.e., pH, glucose, lactate dehydrogenase, bacterial cults) provide essential information for patient management. Therefore, all PPEs should be aspirated for diagnostic purposes. This may require image-guidance if the effusion is small or heavily loculated. According to the current guidelines, any PPE that fulfills at least one of the following criteria should be drained: size ≥ 1/2 of the hemithorax, loculations, pleural fluid pH < 7.20 (or alternatively pleural fluid glucose < 60 mg/dl), positive pleural fluid Gram stain or culture, or purulent appearance. The key components of the treatment of complicated PPE and empyema are the use of appropriate antibiotics, provision of nutritional support, and drainage of the pleural space by one of the following methods: therapeutic thoracentesis, tube thoracostomy, intrapleural fibrinolytics, thoracoscopy with breakdown of adhesions or thoracotomy with decortication. The routine use of intrapleural fibrinolytic therapy remains controversial.

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Derrame pleural paraneumónico y empiema en adultos: guía práctica

Resumen
Alrededor del 20% de los pacientes con neumonía bacteriana tienen derrame pleural. Los derrames pleurales paraneumónicos (DPP) se asocian con una considerable morbilidad. La principal decisión que debe adoptarse en sujetos con DPP es si se requiere la inserción de un tubo de drenaje (DPP complicado). Las pruebas de imagen (radiografía, ecografía y tomografía computarizada) y el análisis del líquido pleural (pH, glucosa, lactato deshidrogenasa, cultivos bacterianos) ofrecen información muy valiosa. Todos los DPP precisan una toracocentesis diagnóstica que, en ocasiones, debe realizarse bajo control ecográfico si el derrame es pequeño o está loculado. Según las guías actuales, se debe drenar cualquier DPP que cumpla alguna de las siguientes condiciones: tamaño ≤ 1/2 hemotórax, presencia de loculaciones, pH < 7,20 (o glucosa < 60 mg/dl), tinción de gram o cultivo positivo o apariencia purulenta. Las bases del tratamiento del DPP complicado y empiema son el uso de antibióticos apropiados, el soporte nutricional y el drenaje del espacio pleural a través de alguno de los siguientes procedimientos: toracocentesis terapéutica, tubo de toracostomía, fibrinolíticos intrapleurales, toracoscopia con rotura de adherencias o toracotomía con decorticación. El empleo rutinario de fibrinolíticos es controvertido.

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Definitions and classification of parapneumonic effusions

A parapneumonic effusion (PPE) refers to any effusion secondary to pneumonia, lung abscess or bronchiectasis. PPEs are divided into three groups: uncomplicated (UPPE), complicated (CPPE) and empyema. An UPPE resolves with antibiotic therapy alone, without pleural space sequelae. A PPE becomes complicated when an invasive procedure, such as tube thoracostomy or surgery, is necessary for its resolution. Empyema is, by definition, pus (i.e., thick, opaque, whitish-yellow, viscous fluid) within the pleural space. Many CPPEs are empyemas, but some PPEs with nonpurulent appearing PF are also CPPEs. Finally, a loculated PPE is an effusion that is not free flowing, whereas a multiloculated PPE is a loculated effusion with more than one compartment.

Pathophysiology

The evolution of a PPE can be divided into three stages that represent a continuous spectrum. First is the exudative stage, characterized by the rapid outpouring of sterile PF

Up to one fourth of exudative pleural effusions occur in association with a pneumonic illness. Community-acquired pneumonia is an important cause of hospitalization and death. There are approximately 4 million cases of community-acquired pneumonia in the United States each year, resulting in about 1 million hospitalizations and 60,000 deaths. The reported rates of accompanying pleural effusion among patients with pneumonia have varied from 10% to 57%, the greater percentages reflecting the use of routine decubitus radiographs. In an earlier prospective study of 203 patients admitted to hospital because of pneumo-nia, 90 (44%) had pleural effusions by bilateral decubitus chest-X rays. However, the effusion was clinically significant (i.e., amenable to diagnostic thoracentesis due to thickness of the pleural fluid [PF] on the lateral decubitus radiograph > 1 cm) only in 37 (18%) cases. In a second study, of the more than 50,000 adult inpatients with community-acquired pneumonia analyzed to develop the Fine’s prediction rule (the Pneumonia Severity Index), about 10% had pleural effusion. In fact, the presence of pleural effusion assigns 10 points to the scoring system used to calculate risk classes II-V of the prediction rule, and is an independent predictor of clinical failure (unresponsiveness to the initial antibiotic treatment) in patients with pneumonia. Finally, in our recent experience with 3,272 patients seen at two Spanish university hospitals for pneumonia, 582 (17.8%) exhibited a pleural effusion on a standard chest radiograph. Our results are in agreement with those of Aliberti et al, who recently reported pleural effusions in 87 of 500 (17.4%) consecutive patients with community-acquired pneumonia.

Risk factors for empyema, the final stage of a parapneumonic effusion, include extreme ages, male sex, debilitation, pneumonia requiring hospitalization, and comorbid diseases, such as diabetes, alcoholism, gastroesophageal reflux disease or chronic obstructive pulmonary disease. Comorbidity was present in 70% of 425 patients with pleural infection in one study. The overall mortality of empyema is 20% at 12 months, and up to 18% of these patients fail to improve with chest tube drainage, antibiotics and fibrinolytics and require a surgical approach. The risk of mortality from empyema is substantially influenced by the presence of comorbid disease. Although most empyemas are secondary to pneumonia, up to 30% are related to a surgical procedure, trauma, esophageal perforation or other causes. This review focuses on the diagnosis and treatment of pleural effusions associated with pneumonia in the adult population.
into the pleural space. The fluid originates in the interstitial spaces of the lung, where it has accumulated because of increased vascular permeability secondary to pro-inflammatory cytokines, and traverses the visceral pleura to enter the pleural space. The PF in this stage is a free-flowing exudate with predominantly polymorphonuclear leukocytes, negative cultures, a glucose level above 60 mg/dl, a pH above 7.20, and a lactate dehydrogenase (LDH) level slightly elevated. If appropriate antibiotic therapy for the underlying pneumonia is instituted at this stage, the pleural effusion progresses no further (UPPE).

If the patient is left untreated for the subsequent days, receives the wrong antibiotic or the inflammation persists within the lung parenchyma, bacteria invade the PF and the second, fibrinopurulent stage, evolves. The normal profibrinolytic state of the pleural cavity is altered and a procoagulable state ensues, allowing the formation of fibrin clots, fibrinous septae, fluid loculation and pleural adhesions. Loculation and septation are not synonymous; the former indicates an effusion that is not free flowing, and the latter indicates the presence of fibrinous septae within the effusion. The PF needs to be drained at this stage (CPPE), but drainage becomes progressively difficult as more loculations form. Diagnostic thoracentesis yields a neutrophilic exudate with low glucose (< 60 mg/dl) and pH (< 7.20) and high LDH levels (> three times the upper limit of normal for serum); PF cultures may be positive. Rarely, fibrinopurulent effusions can have a pH in the normal or even in the alkaline range. For example, if the patient has an infection with Proteus spp., the PF pH may be elevated because these organisms produce ammonia by their urea-splitting ability. Later in the fibrinopurulent stage, as infection progresses, bacteria and inflammatory cells are lysed and pus is formed (empyema).

If a stage 2 effusion is not adequately drained, it progresses to the third stage (organizing stage) in which fibroblasts grow into the pleural space from both the visceral and parietal pleural surfaces, producing a thick pleural peel. This inelastic pleural peel encases the lung and renders it virtually functionless. The use of fibrinolytics at this stage is likely to fail because they may lyse fibrin but not collagenous fibrous tissue. The clinical course after the organizing stage is variable; some patients undergo spontaneous resolution of pleural thickening during the following months, while others develop complications such as lung abscess, bronchopleural fistula and empyema necessitatis (chest wall invasion). Most parapneumonic effusions that enter the organizing stage will require a surgical procedure to establish complete drainage and adequate lung re-expansion.

**Bacteriology**

The bacteriology of pleural infection differs somewhat from that of pneumonia. The most comprehensive report on the bacteriology of CPPE and empyemas comes from one large randomized trial in the United Kingdom: the Multicenter Intrapleural Sepsis Trial 1 (MIST1). In this study of 434 patients with pleural infection, of whom nearly 60% achieved a microbiological diagnosis using standard conventional methods, microbiology showed substantial differences between community-acquired and hospital-acquired infections. The most prevalent organisms cultured in community-acquired pleural infections were streptococcal species (Streptococcus milleri [32%], Streptococcus pneumoniae [13%], other streptococci [7%] followed by anaerobes [16%] and staphylococci [11%]). In contrast, hospital-acquired empyema was dominated by staphylococci (46%), of which 60% were methicillin resistant (MRSA), with most of the remaining caused by gram-negative organisms. Approximately 60% of hospital-acquired infections included bacteria frequently resistant to antibiotics, which has clear implications for empiric antibiotic choices. Of note, one-year mortality was higher in hospital-acquired (47%) than in community-acquired (17%) pleural infections, and in gram-negative (45%), S. aureus (44%) or mixed aerobic infections (46%), compared with streptococcal (17%) and anaerobic (20%) infections. The high frequency of isolation of non-groupable streptococci (viridans or milleri groups) from the PF of patients with community-acquired empyema has been noted in other studies and suggests an oral source.

A recent study showed that the bacteriology of empyema in patients with chronic kidney disease (predialysis) or end-stage renal disease is different from that in the general population. Isolates from the 102 patients with positive culture empyemas (62% secondary to pneumonia) were categorized as community-acquired (n = 62) and hospital-acquired (n = 40). Aerobic gram-negative organisms (68%), especially Klebsiella pneumoniae (31%), rather than the Streptococcus spp. (21%) were the most common pathogens in community-acquired empyema. However, among hospital-acquired empyema, MRSA was still the single predominant organism (25%), as seen in the general population.

** Diagnosis**

Patients with pleural infection most commonly present with the clinical symptoms of pneumonia: fever, cough, sputum production, dyspnea and pleuritic chest pain. The latter may be absent in up to 40% of patients with PPE. The clinical presentation may not be so obvious in the elderly, in immunocompromised patients or in those with an anaerobic pleural infection, who may initially display fatigue, substantial weight loss or altered mental status, without fever or chest symptoms. Many patients with an anaerobic empyema have poor dental hygiene and predisposing factors to aspiration.

The possibility of a PPE should be considered during the initial evaluation of every patient with pneumonia and in any case of pneumonia not responding to antibiotic therapy. The reason for is that a delay in instituting proper pleural drainage in patients with CPPE substantially increases morbidity. In fact, a small free flowing effusion, which is easy to drain, can become large, loculated and difficult to drain over a period of 12 to 24 hours. In one study, the most common causes of early failure (i.e., lack of response or worsening of clinical or radiological status at 48 to 72 hours requiring changes in antibiotic therapy or invasive procedures) in 81 patients hospitalized with community-acquired pneumonia were progressive pneumonia (54 patients, 67%) and pleural empyema (18 patients, 22%).
Imaging of the lung, usually chest radiography, supports the diagnosis of PPE. The typical appearance of a PPE is that of a unilateral pleural effusion associated with an area of consolidation. However, it should be noted that a demonstrable infiltrate by chest radiograph or computed tomography (CT) might not be seen in nearly one third of pleural infections. In these circumstances, nonpneumonic empyemas should be considered in the differential diagnosis, although a true pneumonia in which the pulmonary infiltrate is already resolved or concealed by the passive atelectasis secondary to pleural effusion is an alternative explanation.

The radiographic appearance of PPEs depends upon the amount and the developmental stage of the effusion. If the effusion is uncomplicated, it has the typical arrangement of free PF (i.e., obliteration of costophrenic angles, opacification of the diaphragm and lung base, meniscus sign). If the effusion presents at a later stage, it may be loculated (fig. 1). The appearance of a loculated pleural collection may be rounded and mass-like, and can be confused with pleural or lung malignancy. CPPEs at times may be large and represent the most common nonmalignant etiology (50%) and the second most common overall cause (22%) for pleural effusions occupying ≥ 2/3 of the hemithorax. More than one-third of complicated PPEs and empyemas occupy all or nearly all of the hemithorax.

Patients with pleural effusions > 5 cm in height on a lateral upright chest radiograph (or alternatively > 1 cm in the decubitus position) should undergo thoracentesis to yield material for biochemical and microbiological studies. Portable ultrasound allows not only bedside aspiration, but also the insertion of a thoracostomy tube if necessary.

CT should be ordered whenever a CPPE is suspected, because it provides detailed information about fluid loculation in areas that may escape detection by ultrasound (e.g., paramediastinal region). Empyemas are usually lenticular in shape with enhancement of the thickened inner visceral and outer parietal pleura around the fluid collection ("split pleura sign") (fig. 3). Increased attenuation of extrapleural fat, mediastinal lymphadenopathy greater than 1 cm in diameter, air-fluid levels indicative of bronchopleural fistula, and air bubbles within the fluid collection are other CT findings often seen in patients with empyema. The presence of pleural microbubbles may be associated with an adverse outcome such as the need for repeated drainage or decortication. Chest CT is particularly useful in distinguishing empyema with air-fluid levels from lung abscess.

Plural fluid analysis

Results of thoracentesis drive decisions regarding PF drainage for the majority of patients with PPE. PF samples should be sent for Gram stain, culture, white blood cell count and differential, pH, glucose and LDH, unless they have a purulent appearance. Aspiration of frank pus confirms empyema, and no further tests other than microbiological ones are required, because the need for drainage is universally accepted.

A number of studies have confirmed PF pH, rather than glucose or LDH, as the most useful index predicting the need for tube drainage. In general, a pH < 7.20 or, if pH is unavailable, a glucose < 60 mg/dl or a LDH > three times the upper limit of normal for serum are indications for drainage of the effusion, but these thresholds are not well validated clinically and therefore should not be utilized rigidly. PF for pH should be collected anaerobically with heparin and then measured in a blood gas analyzer. The accuracy of PF pH measurement is critically dependent on sample collection and handling and influenced by variations likely to occur in clinical practice. For example, residual air and analysis delay (> 4 hours at room temperature) causes a significant increase in pH value whereas residual lidocaine re-

Figure 1 Multiloculated pleural effusion. (A) Chest radiograph demonstrating dense rounded opacities with sharp inner margins. (B) Almost complete resolution of the pleural effusion after chest catheter drainage and intracavitary urokinase instillation.
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sults in a decrease\textsuperscript{42}. Measurement of PF glucose is less vulnerable to changes in collection method\textsuperscript{42}. It should be noted that if the pleural effusion is loculated, there might be significant differences in the PF pH from one locule to another\textsuperscript{43}.

Other potential PF markers of nonpurulent CPPE include C-reactive protein, SC5b-9, myeloperoxidase, neutrophil elastase, tumor necrosis factor alpha, interleukin-8, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) or lipopolysaccharide binding protein, but none have gained widespread acceptance\textsuperscript{44}.

More than 40\% of patients with CPPE do not ever have a positive bacterial culture\textsuperscript{17,44}. This may be partly dependent on the use of antibiotics prior to PF sampling and the care with which the PF is handled and cultured, yet another possibility is the presence of severe inflammation without infection. Injecting PF samples into blood culture media containers enhances the diagnostic accuracy of PF cultures\textsuperscript{11}.

Although the yield of PF cultures is particularly low in non-purulent fluids\textsuperscript{45,46}, the impact on management decisions is substantial, in terms of both antibiotic choice and the need for drainage. On the other hand, blood cultures are positive in only a few cases of pleural infection (12\%)\textsuperscript{17}.

The use of new microbiological methods such as nucleic acid amplification and rapid immunochromatographic tests has greatly enhanced the identification of causal bacteria, particularly in patients who have received antibiotics prior to sampling of PF. In a series of 404 parapneumonic effusion samples from the MST1 trial, 17\% of culture-negative cases had bacteria identified by subsequent nucleic acid amplification techniques\textsuperscript{46}. Furthermore, the Binax NOW test for the detection of \textit{S. pneumoniae} antigen, when applied to PF samples, can reveal the pneumococcal etiology of PPE in some patients who have a negative test on urine\textsuperscript{47}.

Identification of complicated parapneumonic effusions

PF parameters and the imaging characteristics of PPEs are used to stratify patients with regard to poor outcome and the need for drainage. According to a consensus statement published by the American College of Chest Physicians (ACCP)\textsuperscript{39}, estimated risk for poor outcome (defined as prolonged hospitalization, prolonged evidence of systemic toxicity, increased morbidity from any drainage procedure, increased risk for residual ventilatory impairment, increased risk for local spread of the inflammatory reaction or increased risk for death) should be the basis for determining whether a PPE should be drained (table 1). The decision to pursue drainage in PPEs depends upon pleural space anatomy, bacteriology, and biochemistry. Category 1 and 2 PPEs generally resolve with antibiotics alone (UPPE). In contrast, the risk of a poor outcome with a category 3 and 4 PPEs is moderate and high, respectively, and these patients should be treated with some form of invasive therapy.

In brief, any PPE that fulfills at least one of the following criteria should be drained: size $\geq \frac{1}{2}$ of the hemithorax, loculations or pleural thickening on imaging studies, PF pH < 7.20 (or alternatively PF glucose < 60 mg/dl), positive PF Gram stain or culture, or purulent appearance\textsuperscript{39}.

A retrospective study involving 240 patients corroborated the usefulness of the ACCP guideline by demonstrating a sensitivity of 97\% and a specificity of 68\%, with regard to predicting which patients with nonpurulent PPEs required drainage\textsuperscript{46}. This study used the clinician’s ultimate decision to drain the pleural cavity as the endpoint; the low specificity reported implies unnecessary drainage in some patients, a misclassification cost that is acceptable from a clinical standpoint.

Differential diagnosis

Sometimes, the gross appearance of the PF is similar in empyema and lipid-rich effusions (chylolithorax, pseudochylothorax, feeding or central venous line infusate). If turbidity remains after centrifugation, it is in all probability due to increased lipid content.

The PF with a PPE is an exudate with a predominance of neutrophils. This biochemical pattern can also be observed in early tuberculosis, malignancy (20\% of cases)\textsuperscript{1}, pulmo-
have anaerobic coverage. Patients with empyema should be treated with antibiotics that are directed at that pathogen. Pathogen-specific therapy should be initiated on the basis of bacterial cultures (blood or PF specimens) or rapid antigen tests for pneumococcus. The optimal duration of antibiotic treatment of CPPE and empyemas is unclear, although it is likely to be at least 3 weeks. Occasionally, there are patients with small sized, acidic or culture positive PPEs who respond well to antibiotic therapy alone.

### Table 1 Categorizing risk of poor outcome in patients with pleural infections

<table>
<thead>
<tr>
<th>Pleural space anatomy</th>
<th>Pleural fluid bacteriology</th>
<th>Pleural fluid pH*</th>
<th>Category</th>
<th>Risk for poor outcome</th>
<th>Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal, free-flowing effusion (&lt; 5 cm on lateral view)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>1</td>
<td>Very low</td>
<td>No</td>
</tr>
<tr>
<td>Small to moderate free-flowing effusion (&gt; 5 cm and &lt; 50% of the hemithorax)</td>
<td>Negative results</td>
<td>≥ 7.20</td>
<td>2</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>Large, free-flowing effusion (≥ 50% of the hemithorax) or loculated configuration</td>
<td>Positive Gram stain or culture</td>
<td>&lt; 7.20</td>
<td>3</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Irrelevant</td>
<td>Finding of pus</td>
<td></td>
<td>High</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Modified from the American College of Chest Physicians’ consensus statement.

*If pH is not available, pleural fluid glucose with a cutoff 60 mg/dl should be used.

### Treatment

Many patients with PPE do not require a treatment different from that of underlying pneumonia. In the series of Light et al., in which thoracentesis was performed in 37 (41%) of 90 patients with PPE, only 10 (27%) had CPPE. Even so, of 398 patients with pleural infection who underwent a diagnostic thoracentesis in two different Spanish hospitals, pleural space drainage was mandatory in 62%. Drainage can be accomplished in one of three ways: chest tube, intrapleural fibrinolytics through tube thoracostomy or surgical debridement. In any case, a definitive therapeutic option should be performed within the first two weeks of hospitalization.

### Antibiotics

All patients with PPE should receive antibiotics, which are selected according to the current guidelines for treatment of pneumonia. If the etiology of PPE has been identified on the basis of bacterial cultures (blood or PF specimens) or rapid antigen tests for *S. pneumoniae* (urine or PF specimens), antimicrobial therapy should be directed at that pathogen. Patients with empyema should be treated with antibiotics that have anaerobic coverage. Aminoglycosides are not recommended in empyema because of their poor penetration into the pleural space and inactivation in acidic environments. A suggested regimen for community-acquired empyema is amoxicillin-clavulanate. However, in penicillin allergic patients, either meropenem or moxifloxacin can be used as an alternative treatment. For patients with hospital-acquired empyema, empirical therapy with meropenem or piperacillin/tazobactam plus linezolid covers the most likely pathogens. The optimal duration of antibiotic treatment of CPPE and empyemas is unclear, although it is likely to be at least 3 weeks. Occasionally, there are patients with small sized, acidic or culture positive PPEs who respond well to antibiotic therapy alone.

### Nutrition

Patients with empyema suffer the protracted catabolic consequences of chronic infection and are often malnourished. A low serum albumin is associated with a poor prognosis. It is therefore essential to provide adequate nutritional support from the time of diagnosis. This may require supplementary nasogastric feeding or even parenteral nutrition.

### Therapeutic thoracentesis

In patients with a moderate sized PPE involving one fourth or less of the hemithorax (i.e., sufficient to warrant thoracentesis), a therapeutic, rather than a diagnostic pleural aspiration, can be an initial treatment option, provided the pleural space is not purulent. The rationale behind this recommendation is that it can be technically difficult to insert a chest tube in such small PPEs, and if no fluid reaccumulates after the initial therapeutic thoracentesis, one need not worry about the PPE as long as the patient is doing well.

### Chest tube drainage

Current indications for intercostal tube drainage have already been stated (vide supra). It should be emphasized that it is better to place some unnecessary chest tubes than leave a PPE undrained and at risk for empyema formation. This is particularly true in the presence of some clinical features, such as the persistence of fever, failure of the acute-phase reactants to drop, advanced age or comorbidity.

Traditionally, large-bore chest tubes (> 20 F) placed without imaging by thoracic surgeons have been recommended for draining empyema because of the belief that smaller
tubes would become obstructed with the thick fluid. However, small-bore catheters (8-14 F) inserted with the Seldinger technique under bedside ultrasound or CT guidance are more frequently used today\cite{60,51}. Their success is comparable to standard chest tubes in most series, and they are easier and less traumatic to insert and better tolerated by patients\cite{59}. The sum of three series, totaling 248 patients with empyema, shows that small-catheters with or without intrapleural fibrinolysis served as the definitive treatment in 84% of cases\cite{52-54}. Nevertheless, we prefer to avoid the use of the smallest catheters (< 12 F) for CPPEs due to their higher rates of blockage\cite{34}.

Once a chest catheter has been positioned into a dependent part of the pleural effusion, it is connected to a commercially available underwater-seal drainage system. To maintain patency of small-bore catheters (particularly if 8-10 F), regular flushing with 20 ml sterile saline via a three-way tap is recommended (e.g., twice daily) and suction can be applied to improve drainage\cite{16}. The patient’s clinical status, tube output, and chest radiographs should be reviewed daily to determine the effectiveness of drainage\cite{26}. If drainage is inadequate, a chest CT scan should be obtained to find out whether the tube is mispositioned\cite{29} or whether there are loculations that warrant the instillation of intrapleural fibrinolytics or an entrapped lung. Kinking and dislodgement of the chest catheter are also causes of unsuccessful drainage. In general, the drain is removed when there is clinical improvement, radiological resolution of the effusion and the volume of output flow is less than 100 ml/day\cite{26}.

**Intrapleural fibrinolytics**

Fibrinolytic agents including streptokinase, urokinase and alteplase (t-PA), offer the possibility of dissolving fibrous septa, unifying the pleural space and rendering a multi-loculated collection amenable to drainage via a single catheter\cite{16}. The daily administration of these agents, for a period of 1 to 6 days, is as follows: streptokinase 250,000 IU; urokinase 100,000 IU; and alteplase 10 mg. These medications are diluted in 50 ml of sterile saline and instilled through the chest tube, which is immediately clamped for two hours before returning to normal drainage. Although generally safe, potential side effects of intrapleural administration of fibrinolytics include chest pain, fever, allergic reactions (streptokinase), and pleural hemorrhage\cite{29}. To date, it remains unknown if streptokinase administered intrapleurally will generate a systemic antibody response that will neutralize its therapeutic effects when given intravenously in the future for an ST-segment elevation myocardial infarction.

The largest randomized trial to date on the use of intrapleural fibrinolytics for treating CPPE and empyema (MIST1) could not substantiate the efficacy of this treatment modality\cite{9}. In this study, 454 patients with pleural infection (defined by the presence of purulent PF, culture-positive PF or PF with a pH < 7.2) were randomly assigned to receive intrapleural streptokinase or saline placebo. There was no benefit to streptokinase in terms of mortality, need for surgery, radiographic outcome, or length of hospitalization\cite{9}. However, a recent meta-analysis of seven randomized controlled trials, including the MIST1, with a total of 761 participants with empyema or loculated PPE concluded that intrapleural fibrinolytic therapy (streptokinase or urokinase) confers significant benefit in reducing the requirement for surgical intervention, but has no effect on the risk of death\cite{35}. Authors admitted that, for uncertain reasons, there was discordance between earlier positive studies and the more recent negative study by Maskell et al\cite{9}.

An ongoing multicenter trial (MIST2) will shortly assess the possible benefits of combined human recombinant deoxyribonuclease (DNase) and alteplase in pleural infections based on the hypothesis that they might work synergistically: the DNase would reduce the effusion viscosity and the fibrinolytic would break down the loculations. Until the results of this study become available, there still seems to be a place for fibrinolytics in the early management of loculated PPE and empyema as a trial before committing the patient to surgery. Fibrinolytics are best used when the patient is not a candidate for surgery or when an experienced thoracoscopist is not readily available.

**Surgery**

Patients who are not making clinical progress within 7 days despite appropriate antibiotics and chest tube drainage or intrapleural fibrinolytics should be considered for surgery\cite{25}. In the MIST1 trial, 15% of 427 patients required surgical drainage of the infected pleural space during the three months after randomization\cite{9}. Among the surgical options available, the use of video assisted thoracoscopic surgery (VATS) has become widespread\cite{26}. With VATS, the loculi and adhesions in the pleural space can be disrupted, the pleural space completely drained, the chest tube optimally placed, and if the lung is trapped, an attempt can be made to perform a decortication\cite{26}. This technique requires general anesthesia, single-lung ventilation, operator expertise and availability. For the treatment of CPPE and empyema, it has a success rate of more than 80% and a mortality rate of 2-3%\cite{60,62}.

Another way of disrupting the fibrin membranes producing loculations is with medical thoracoscopy, whose main advantage over VATS is that the examination can be performed under local anesthesia and conscious sedation. This was demonstrated in a retrospective study of 127 patients, of whom 94% were treated successfully for multiloculated empyema\cite{35}. However, this treatment should only be carried out early in the course of CPPE and empyema, before the adhesions become too fibrous.

Open thoracotomy with decortication (i.e., stripping of the visceral pleural peel and evacuation of pus and fibrous tissue from the pleural cavity) is indicated for the treatment of empyema in the organizing stage\cite{35}. Despite success rates of around 95% it is a major thoracic operation with an associated mortality of 10% and substantial morbidity (e.g., post-thoracotomy pain)\cite{59,61}. Therefore, it should not be performed in patients who are markedly debilitated.

In high risk patients unfit for general anesthesia but with persistent pleural infection, meticulous CT guided placement of small catheters and intrapleural instillation of fibrinolytics into the pockets can be attempted. Alternatively, the empyema can be drained by the creation of a pleural window by means of rib resection performed under local anesthesia\cite{25}.
Figure 4 proposes a stepwise approach for managing patients with PPE, which moves from the less invasive to the more invasive treatments.

**Outcome**

The morbidity and mortality rates in patients with PPE are higher than those in patients with pneumonia alone. It is generally accepted that the need for pleural drainage and the presence of an underlying disease predict a longer hospital stay\(^6\). A multivariate logistic regression analysis from the MIS T1 trial has shown that the following features at presentation are associated with poor outcome, which is defined as high risk of death (RAPID score)\(^6\): Renal profile (urea > 7 mmol/l), Age ≥ 65 years, Protein (albumin < 25 g/l), In-patient empyema, and Diastolic blood pressure < 70 mm Hg. Each item adds 1 point to the total score. Patients with a score 2 had a low mortality (1-3%); those with a score of 3 had an intermediate mortality (25%); whereas 4 or 5 points implied a high risk of death (68%). This model needs to be validated in other cohorts before it can be used as a clinical tool.

Finally, in two Spanish series, comprising 506 patients with PPE, residual pleural thickening (i.e., pleural thickness ≥ 10 mm in a chest radiograph) was found to occur in 20% of patients at 6 months\(^22,67\). Risk factors for its development included purulent PF and delayed (> 15 days) resolution of PPE. However, pleural thickening was not associated with functional impairment (Anexo).

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**ANEXO: AUTOEVALUACIÓN**

Pretende ser un instrumento de formación continuada. Al finalizar cada Actualización Clínica, el lector dispondrá de 4 o 5 preguntas de elección múltiple, sólo una de las cuales es correcta. Las preguntas han sido elaboradas por los autores de la Actualización Clínica.

1. ¿Cuál de las siguientes afirmaciones es falsa?
   a) El 20% de los pacientes con neumonía tienen un derrame pleural asociado
   b) Cuando una neumonía no responde al tratamiento antibiótico se debe considerar la posibilidad de un derrame paraneumónico
   c) El 70% de los empiemas son secundarios a una neumonía
   d) No todos los derrames paraneumomícicos complicados son empiemas
   e) Más de un tercio de los empiemas requerirá tratamiento quirúrgico

2. ¿Qué germen se aisla más comúnmente en pacientes con empiema adquirido en la comunidad?
   a) Estreptococos no clasificables (*milleri, viridans*)
   b) Neumococo
   c) Anaerobios
   d) Estafilococo dorado sensible a oxacilina
   e) Estafilococo dorado resistente a oxacilina

3. ¿Cuál de los siguientes regímenes antibióticos indicaría de forma empírica ante un paciente con empiema adquirido en el hospital?
   a) Amoxicilina-clavulánico
   b) Levofloxacino
   c) Ceftriaxona y azitromicina
   d) Piperacilina-tazobactam y linezolid
   e) Ceftazidima y gentamicina

4. Un paciente de 58 años ingresa por una neumonía adquirida en la comunidad. Al segundo día se detecta un derrame pleural derecho que ocupa el 60% del hemitórax. ¿Cuál sería su actitud terapéutica?
   a) Continuar con antibióticos y esperar la evolución
   b) Cambiar el esquema antibiótico
   c) Colocar un tubo de drenaje torácico y analizar el líquido extraído
   d) Analizar el líquido y colocar un tubo sólo si se evidencia pus
   e) Analizar el líquido y colocar un tubo sólo si el cultivo bacteriano es positivo

5. ¿En cuál de las siguientes circunstancias indicaría la colocación de un tubo de drenaje torácico en un paciente con derrame paraneumónico?
   a) El derrame pleural está loculado
   b) El pH del líquido pleural es < 7,20
   c) La glucosa del líquido pleural es < 60 mg/dl
   d) El cultivo del líquido pleural es positivo
   e) En todas las anteriores

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Figure 4 A stepwise approach to parapneumonic effusions. CT: computed tomography; PF: pleural fluid; US: ultrasound; VATS: video-assisted thoracic surgery.
References


24. Parapneumonic pleural effusions and empyema in adults: current practice. 493


