New trends in the diagnosis and treatment in parapneumonic effusion and empyema

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SUMMARY

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Despite treatment with antibiotics, patients with complicated parapneumonic effusion (PPE) and empyema have an increased morbidity and mortality due at least in part to inappropriate management of the pleural effusion. PPE should be considered in all patients with pneumonia as antibiotic therapy is being initiated. If the diaphragms cannot be seen throughout their length on the chest radiographs, a lateral decubitus radiograph, ultrasonography or computerized tomography scan should be obtained. If the effusion is more than 10 mm in thickness, a therapeutic thoracentesis should be performed. If the fluid cannot all be removed and the characteristics of the pleural fluid indicate a poor prognosis, a chest tube should be inserted. If the drainage is incomplete due to loculation of the PPE intrapleural fibrinolytics or thoracoscopy should be performed. If the lung does not reexpand completely with thoracoscopy, then decortication should be performed without delay.

Key Words: Parapneumonic effusion, empyema.
Clinical Manifestations

The clinical manifestations of PPE and empyema depend to a large part on whether the patient has an aerobic or an anaerobic infection. The clinical presentation of patients with aerobic bacterial pneumonia and PPE is no different from that of patients with bacterial pneumonia without PPE. The patients first manifest an acute febrile illness with chest pain, sputum production, and leukocytosis. Infections with anaerobes are more likely to have an insidious clinical onset, with less fever, greater weight loss, and are more common in patients who are alcoholics, have had an episode of unconsciousness or who have poor dental hygiene (13).

Radiological Examination

Chest radiography: The presence of a significant amount of pleural fluid is usually suggested on the lateral view where the posterior costophrenic angle is blunted or one of the diaphragms is not visible throughout its length (14). All patients with pneumonia should have a lateral view. However, the sensitivity of posteroanterior and/or lateral view for detecting pleural fluid was 80% in parapneumonic effusions diagnosed with lateral decubitus view (15). The amount of free pleural fluid can be semiquantitated by measuring the distance between the inside of the chest wall and the outside of the lung on a lateral decubitus view. The positive predictive value of lateral decubitus view for pleural effusion was 92% in patients diagnosed with USG (16). If this distance measures less than 10 mm, the pleural effusion is not clinically significant and a thoracentesis is not indicated as the pleural effusion will resolve with antibiotics alone (1) (Table 2).

Table 2. A classification and treatment scheme for PPE and empyema.

<table>
<thead>
<tr>
<th>Class</th>
<th>pH, Glucose and LDH level</th>
<th>Gram stain and culture or frank pus</th>
<th>Loculation</th>
<th>Treatment in addition to antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nonsignificant pleural effusion</td>
<td></td>
<td></td>
<td>Antibiotics only</td>
</tr>
<tr>
<td>2</td>
<td>Typical parapneumonic pleural effusion</td>
<td>pH &gt; 7.2, Glucose &gt; 40 mg/dL, LDH &lt; 3 x upper limit normal for serum</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Borderline complicated pleural effusion</td>
<td>7.0 &lt; pH &lt; 7.2 and/or Glucose &gt; 40 mg/dL and LDH &gt; 3 x upper limit normal for serum</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Simple complicated pleural effusion</td>
<td>pH &lt; 7.0 or Glucose &lt; 40 mg/dL</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Complex complicated pleural effusion</td>
<td>pH &lt; 7.0 and/or Glucose &lt; 40 mg/dL</td>
<td>Positive</td>
<td>Multiple</td>
</tr>
<tr>
<td>6</td>
<td>Simple empyema</td>
<td>pH &lt; 7.0</td>
<td>Frank pus</td>
<td>Single or free flowing</td>
</tr>
<tr>
<td>7</td>
<td>Complex empyema</td>
<td>pH &lt; 7.0</td>
<td>Frank pus</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

Nonsignificant pleural effusion, small effusions less than 10 mm thickness on decubitus chest radiography is not necessary for the thoracentesis.
Ultrasonography (USG): The amount of pleural fluid can be semiquantitated with USG. Ultrasound can also demonstrate whether septations are present within loculations (17).

Chest computed tomography (CT): Contrast-enhanced thoracic CT provides detailed information about how much of the increased density on a chest radiograph is due to pleural fluid and how much is due to parenchymal infiltrate. It also demonstrates fluid loculation (but not septations), pinpoints the position of existing chest tubes, help to differentiate pleural empyema from a lung abscess and can identify any airway obstruction caused by tumor or foreign body (2). High resolution CT scan is not indicated as it adds nothing to the regular CT scan in this situation.

Thoracentesis
If the thickness of the fluid is greater than 10 mm on the decubitus radiograph or on the USG examination, a therapeutic thoracentesis rather than a diagnostic thoracentesis with a needle-catheter system should be performed immediately because it is impossible to separate complicated from uncomplicated effusions without a thoracentesis (1). If the fluid does not reaccumulate, one need not worry about the PPE. USG is particularly well suited for guiding pleural interventions. It increases the success rate and reduces complications of thoracentesis (18).

Analysis of Pleural Fluid
The pleural fluid should be sent for Gram stain and bacterial culture, white blood cell count and differential, and for determination of its level of glucose, LDH, and pH. In the diagnosis of complicated PPE, the demonstration of a threshold of a pH < 7.2 is most important. Other pleural fluid parameters such as reduced glucose (< 40 mg/dL) or elevated LDH (> 3 times the upper limit of normal) may support the diagnosis of complicated PPE, although these are less useful diagnostically than the pleural fluid pH (19). The pH should be measured with a blood gas analyzer, not a pH meter or an indicator tape (3). In a given patient with loculated pleural fluid, there can be variations in pH, glucose and LDH between different locules (20). The diagnostic yield from the bacterial cultures will be increased if the pleural fluid is inoculated into blood culture bottles at the bedside (21).

Recent studies have reported that pleural fluid TNF-α levels, myeloperoxidase levels and polymorphonuclear elastase levels are higher in complicated PPE and empyema than in uncomplicated PPE, but additional studies are necessary to determine the rightful place of these tests in the management of PPE (22-24).

TREATMENT
Despite of effective antibiotics and drainage of the infected pleural fluid, the overall mortality rates of empyema is as high as 20% (11). The management of PPE and empyemas involves two separate areas-selection of an appropriate antibiotic and management of the pleural fluid (1).

I. Antibiotics Treatment
All patients with PPE or empyema should be empirically treated with intravenous antibiotics as initial therapy for hospitalized patients. If the Gram stain of the pleural fluid is positive, it should guide the selection of an antibiotic. The recent common microorganisms of complicated PPE and empyema are *Streptococcus milleri* group, *Streptococcus pneumoniae*, other streptococci, Enterobacteriaceae, anaerobic bacteria, *Staphylococcus aureus* including methicillin-resistant, and enterococci (25). The initial antibiotic selection is not influenced by the presence or absence of pleural effusion, and usually based on whether the pneumonia is a community-acquired or a hospital-acquired and how sick the patient is (1). Because anaerobes are difficult to culture and often coexist with aerobes, additional empirical treatment of anaerobes should be considered. Beta-lactam show good penetration of the pleural space (26). However, aminoglycosides appear to penetrate poorly into purulent pleural fluid and are less active at an acid pH and are not usually recommended except infection with *Pseudomonas aeruginosa*. Because atypical pathogens like as *Legionella pneumophila* or *Mycoplasma pneumoniae* rarely lead to empyema, macrolide should only be ad-
ded in suspected case (2). New antibacterials used in treatment of community-acquired pneumonia like the respiratory fluoroquinolones or telithromycin have not been not adequately studied in PPE or empyema.

In patients with community-acquired PPE or empyema, a beta-lactam (cefotaxime, ceftriaxone) plus metronidazole or beta-lactamase inhibitor (amoxicillin-clavulanate, ampicillin-sulbactam) are recommended (28). For patients allergic to both penicillin and cephalosporins, combinations such as ciprofloxacin and clindamycin may be effective (2). In patients with hospital acquired and severe community-acquired PPE or empyema, the antibiotics should be chosen to treat both gram-positive and gram-negative aerobes and also anaerobes. Recommended antibiotics include anti-pseudomonal beta-lactam (cefepime) plus metronidazole or beta-lactamase inhibitor (piperacillin-tazobactam), or anti-pseudomonal carbapenem (imipenem, meropenem) with anti-pseudomonal fluoroquinolone (ciprofloxacin, levofloxacin) or aminoglycoside (26,28,29). Anti-staphylococcal coverage including methicillin resistant Staphylococcus aureus (vancomycin or linzolid) is often required (28).

The optimal duration of antibiotic treatment is unclear, although it is likely to be at least 3 weeks. Measurement of inflammatory markers such as serum C-reactive protein, in addition to clinical assessment, may provide a useful guide to treatment response (1).

II. Management of Pleural Fluid

There are several treatment options available for the management of the pleural fluid in patients with complicated PPE and these include repeated therapeutic thoracentesis, tube thoracostomy, intrapleural instillation of fibrinolytics, video-assisted thoracoscopic surgery (VATS) with the breakdown of adhesions, thoracotomy with decortication and the breakdown of adhesions, and open drainage (1). Patients with class 5, 6, and 7 effusions will often require thoracoscopy or thoracotomy for complete drainage and adequate lung re-expansion (Table 2) (19).

Chest Tube Thoracostomy

Findings that indicate that tube thoracostomy will be necessary for resolution of a PPE are listed in Table 1 (1,2). Patients with characteristics higher in Table 1 are more likely to need tube thoracostomy or some other invasive procedure. Successful closed-tube drainage of complicated PPE is evidenced by improvement in the clinical and radiological status within 24 hours (3). In general, chest tubes should be left in place until the volume of the pleural drainage is under 50 mL for 24 hours and until the draining fluid becomes clear yellow.

What sized tube should be used?

In the past, relatively large (28 to 36F) tubes have been recommended owing to the belief that smaller tubes would become obstructed with the thick viscous fluid. Small catheters (6 to 14F) pigtail or Malecot served as the definitive treatment in 78% of patients and had the advantages that they were easier to insert and less painful (30). In cases where small sized catheters are used, the use of suction (20 cmH2O) and regularly flushes (eg, 30 mL normal saline every 6 hours) may help to prevent their occlusion (2).

What next if tube fails?

The failure rate associated with primary intervention using tube thoracostomy is at least 40% (31). If the patient is not improving with chest tube drainage, either the patient is receiving the wrong antibiotics agent or the drainage is inadequate that can be caused by poor positioning of the chest tube, obstruction or kinking of the chest tube, loculated or inaccessible pleural fluid, or the presence of highly viscous fluid (3). If the chest tube is occluded attempts should be made to restore its patency with saline flushes or the intratubal injection of tissue plasminogen activator (tPA), or the tube should be removed to prevent pleural superinfection (2).

Fibrinolytic Treatment

The intrapleural administration of fibrinolytic agents has been used to aid the drainage of infected pleural fluids with the hope that this will reduce the need of surgery for over 50 years.
The use of fibrinolytics is recommended by management guidelines (2,31). The theory behind their use is that loculations in the pleural space are produced by fibrin membranes; intrapleural fibrinolytics may dissolve the fibrin membranes and facilitate drainage of the pleural space (3). The intrapleural fibrinolytic agents that used mostly, are streptokinase (SK) 250,000 IU and urokinase (UK) 100,000 IU for 3 days.

Is the streptokinase effective management?

In three earlier randomized controlled trials, patients treated with intrapleural SK appeared to have benefit by having a higher total volume of pleural fluid drained, greater chest radiograph improvement, higher clinical success rate, fewer referrals for surgical interventions (VATS or open decortication), and decreased length of hospital stay (32-34). These three studies had low statistical power because of the small number of patients included. In a recent randomized multicenter trial of 427 patients by Maskell et al., the intrapleural administration of SK did not improve mortality, the rate of surgery, or the length of the hospital stay (25). In view of this latter study, SK should only be considered if the patient refuses surgery or is too sick for surgery. At the present time, SK is unavailable in the United States.

How about urokinase?

In one randomized trial of intrapleural UK, there was a statistically significant benefit in mean time to defervescence, duration of hospitalization, duration of pleural fluid drainage, total fluid drained, and improvement in chest radiographs with no significant side effects (35). More randomized studies in large number may be needed.

Are there any new agents?

The patients that received alteplase, recombinant tPA, had more pleural fluid drainage than UK with similar overall success rates (36). When tPA was administered within 24 hours of diagnosis, the amount of pleural fluid drainage was higher and there was a shorter duration of chest tube drainage than after 24 hours of diagnosis (37). It will be an effective treatment for loculated PPE.

In a single case report, use of intrapleural human recombinant DNase (Pulmozyme) was successful in the treatment of empyema following failure of SK (38). At the present time, there is a multicenter study in the United Kingdom where patients with multiloculated PPE are randomized to saline, tPA, DNase or tPA plus DNase.

Surgery

When medical treatment fails, surgical intervention should be considered without further delay. Failure of medical treatment is indicated by clinical evidence that the sepsis syndrome has progressed or persisted (i.e., there is fever, leukocytosis, and/or elevated C-reactive protein) and by the presence of significant residual pleural fluid. Lim et al. reported that an empirical treatment strategy which combines adjunctive intrapleural fibrinolysis with early surgical intervention results in shorter hospital stays and may reduce mortality in patients with pleural sepsis (39). Kalfa et al. reported that thoracoscopy within four days of diagnosis was associated with a shorter operative time and postoperative hospital stay, fewer technical difficulties, fewer complications, and no need for other surgical procedures (40).

Video assisted thoracoscopic surgery (VATS): VATS is less invasive than open thoracotomy and is associated with less patient discomfort and less severe pain compared with thoracotomy. In a randomized controlled study of 20 patients with pleural infection, Wait et al. reported that early immediate treatment with VATS compared with intrapleural SK resulted in higher primary treatment success, shorter drainage time, shorter hospital stay, and similar costs (41). Luh et al. reported recently that 202 of 234 patients (86.3%) achieved satisfactory results with VATS treatment (42). Multiloculated empyema can also be treated with medical thoracoscopy. Brutsche et al. recently reported in a retrospective study that 119 of 127 patients (91%) were healed by medical thoracoscopy, and the median duration of chest tube drainage post medical thoracoscopy was seven days (43).

Thoracotomy with decortication: With this procedure, which involves a full thoracotomy, all the fibrous tissue is removed from the visceral pleura and all pus is evacuated from the pleural
space. Decortication eliminates the pleural sepsis and allows the underlying lung to expand (3).

**Open drainage by rib resection:** Chronic drainage of the pleural space can be achieved with open drainage procedures. In general open drainage procedures are recommended only for patients who are debilitated and not candidates for thoracoscopy or thoracotomy.

**RECOMMENDED MANAGEMENT of PARAPNEUMONIC EFFUSIONS**

It is recommended that a stepwise approach be taken for patients with PPE (Figure 1). When a patient with pneumonia is initially evaluated, the possibility of a PPE should be assessed. If pleural fluid is present and its thickness is more than 10 mm, a thoracentesis (a therapeutic rather than a diagnostic thoracentesis) should be performed without delay. If the fluid reaccumulates after initial thoracentesis, a second therapeutic thoracentesis should be performed if poor prognostic factors were present, and if the fluid reaccumulates after second thoracentesis, a tube thoracostomy should be performed if poor prognostic factors are present. If the pleural fluid is loculated, then more aggressive therapy is indicated. If the therapeutic response with thoracostomy is inadequate, a CT scan of the chest should be obtained and fibrinolytics may be used. However, if complete drainage is not obtained with one or two administrations of the fibrinolytics, one should move to thoracoscopy. If with thoracostomy, the lung does not reexpand completely, then decortication should be performed without delay. Open drainage procedures are reserved for those patients who are too ill to undergo thoracoscopy or thoracotomy. The definitive treatment should be performed within the first 10 days of hospitalization.

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