Management of Pleural Space: Effusions and Empyema

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KEYWORDS

• Pleural effusion • Pleurodesis • Empyema • Thoracoscopy
• Fibrinolysis

Surgeons are commonly called on to evaluate patients with pleural effusions. This article discusses the normal anatomy, physiology, and pathophysiology of the pleural space. The signs and symptoms of pleural effusions as well as the evaluation of pleural effusions of unknown cause are also reviewed. Although pleural effusions can be seen in a host of medical disorders, the 2 main circumstances that the surgeon is involved with are with malignant pleural effusions and pleural sepsis and therefore the management of theses 2 entities is discussed in detail.

PLEURAL SPACE PHYSIOLOGY

The pleural space lies between the visceral and parietal pleura and consists of 2 opposed pleural surfaces separated by 10 to 20 μm of glycoprotein-rich fluid. The normal volume of pleural fluid is low, at approximately 10 mL (0.1–0.2 mL/kg body weight). Pleural fluid contains few cells under normal circumstances.[1] The normal pleura is a thin translucent membrane and consists of 5 layers: (1) the mesothelium (flattened mesothelial cells joined primarily by tight junctions); (2) submesothelial connective tissue; (3) a superficial elastic layer; (4) a second loose subpleural connective tissue layer rich in arteries, veins, and nerves; (5) a deep fibroelastic layer adherent to the underlying lung parenchyma, chest wall, and diaphragm or mediastinum.[2]

The parietal pleura derives its blood supply from branches of the intercostal arteries. The mediastinal pleura is supplied by the pericardiophrenic artery and the diaphragmatic pleura from the superior phrenic and musculophrenic arteries. The visceral pleura derives most of its blood supply from the bronchial arterial system.[2]

There exist naturally occurring pores, or stomata, in the caudal portion of the parietal pleura and lower mediastinal pleura that are capable of transferring particulate matter

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and cells directly into lymphatic channels for removal. Most of the fluid that accumulates abnormally in the pleural space is derived from the lung through the visceral pleura and is absorbed primarily thorough the parietal pleura.[3] In disease states, excess production and/or decreased absorption of lymph is responsible for the generation of effusions.

Evaluation of Pleural Effusions

Causes of effusions are manifold. They can be classified as transudative with a low protein content (found in congestive heart failure, cirrhosis, nephrotic syndrome) or as exudative with a high protein content (found in cancer, infection, pulmonary emboli, pancreatitis, collagen vascular disease, drug-induced conditions, hemothorax, chylothorax).[4]

The clinical scenario is helpful in determining the cause of an effusion. Signs or symptoms of infection, history of malignancy, or associated medical diseases such as cardiac failure or kidney or liver disease can be helpful in determining the cause of an effusion.

Small pleural effusions are asymptomatic. Large pleural effusions can cause dyspnea, cough, and chest discomfort.

Effusions are generally seen on chest radiograph. Small pleural effusions may be evident as blunting of the costophrenic angle. A lateral decubitus film can confirm an effusion to be free flowing. Loculated effusions are harder to diagnose on a standard chest radiograph. Ultrasound can detect a loculated effusion and also determine an appropriate site for thoracentesis. A computed axial tomography (CAT) scan is useful in the evaluation of pleural effusions. It can determine the size and the location of the effusion and it also gives information regarding associated underlying parenchymal and pleural abnormalities.

Thoracentesis is useful to determine the cause of an effusion. Pleural fluid evaluation should include cytologic evaluation, culture, cell count, and differential and simultaneous pleural fluid and serum protein, glucose and lactate dehydrogenase (LDH) levels. Effusions are classified as exudative or transudative based on protein and LDH levels. (Exudate = pleural fluid protein/serum protein >0.5 and pleural fluid LDH/serum LDH >0.6.[4]) Malignant cells on cytologic evaluation indicate an underlying malignancy causing the effusion. Although the specificity of cytologic analysis is high, the sensitivity of a single cytologic evaluation can be as low as 50% and therefore often more invasive procedures may be required to diagnose an underlying malignancy, as discussed later.[5] Presence of an increased white blood cell count in the pleural fluid, particularly with a preponderance of neutrophils, may indicate pleural infection. Low pleural fluid glucose and pH are indicators of active pleural infection and the need for pleural drainage, as discussed in detail later.

A transudative effusion occurs most commonly secondary to congestive heart failure. Transudative effusions are generally managed by medical therapy for the underlying disease. Occasionally another intervention, such as pleurodesis, is required in cases refractory to maximal medical therapy. There are multiple causes for exudative effusions, but they are most commonly due to malignancy, infection, or pulmonary emboli. Overall, the 4 most common causes of pleural effusions in the United States are congestive heart failure, bacterial pneumonia, malignancy, and pulmonary emboli.[4]

Patients in whom a diagnosis of pleural effusion has not been ascertained after thoracentesis and CAT scan should undergo thoracoscopy and bronchosopy. Thoracoscopy allows direct pleural biopsy and also the potential for therapeutic intervention, including evacuation of the effusion either with or without pleurodesis.

The rest of this article focuses on the management of malignant pleural effusions, parapneumonic effusions, and empyema.

Malignant Pleural Effusions

Malignant pleural effusions cause dyspnea and decreased exercise tolerance, and may significantly affect a patient's quality of life. Approximately half of all patients with metastatic cancer develop a pleural effusion.[6] Drainage of pleural fluid with reexpansion of underlying lung can provide impressive relief of dyspnea and a significant improvement in the patient's overall sense of well-being.

Increased capillary permeability in patients with advanced cancer may result in increased pleural fluid production and simultaneously lymphatic obstruction by metastatic disease may result in decreased pleural fluid drainage. This imbalance between production and drainage of pleural fluid results in the development of a pleural effusion. Tumor cells in the pleural fluid also may contribute to pleural fluid accumulation by increasing the pleural osmotic pressure.[6]

Two general approaches exist for the management of symptomatic malignant pleural effusions: drainage and pleurodesis, or placement of a long-term pleural catheter for intermittent drainage at home. Thoracentesis alone should be offered as a therapeutic option only for patients in whom survival is expected to be short, or in the rare patient with a slowly reaccumulating malignant pleural effusion.

Pleurodesis is a treatment that aims to produce fibrosis of the pleura by chemical or mechanical means to obliterate the pleural space. The aim of pleurodesis in patients with malignant effusions is to prevent reaccumulation of the effusion after drainage, thereby permanently alleviating the associated symptoms. For successful pleurodesis to be achieved, the parietal and visceral pleura must be in apposition. In those patients in whom the lung incompletely reexpands after pleural fluid drainage pleurodesis is not successful. This condition is referred to as a trapped lung. Incomplete lung reexpansion after drainage of a malignant pleural effusion should be viewed as a contraindication to attempted sclerosis and is an indication to pursue alternative therapeutic options such as placement of a long-term indwelling pleural catheter. Furthermore, for pleurodesis to be successful, the patient must be able to mount an inflammatory response sufficient to fuse the pleural space. The use of antiinflammatory medications should be avoided in patients undergoing pleurodesis.

Sclerosing agents are instilled into the pleural space to induce pleurodesis. Multiple agents have been tried for this purpose. Shaw and Agarwal[6] reviewed studies comparing different sclerosants in an attempt to obtain pleurodesis in the Cochrane Database in 2009. Comparing different sclerosants, talc was found to be the most efficacious. The relative risk of nonrecurrence was 1.34 (95% confidence interval [CI] 1.16–1.55) in favor of talc compared with bleomycin, tetracycline, mustine, or tube drainage alone based on 10 randomized controlled studies involving 308 patients. In most studies the efficacy of talc was judged by radiographic evidence for the recurrence of an effusion or clinical need for repeat thoracenteses. Three studies compared talc with tetracycline with 103 participants and the relative risk of success favored talc at 1.32 (95% CI 1.10–1.72). Typically 5 g of talc are instilled into the pleural space to induce pleurosesis; either as a suspension in 50 to 100 mL normal saline via a chest tube, or via direct insufflation at thoracoscopy.

Some investigators have reported the development of acute lung injury after pleural talc instillation that can be associated with severe respiratory insufficiency and death. It seems to be related to the size of talc particles, and administration of filtered talc with uniform small particles is recommended.[7]

Currently most physicians base the decision of when to remove the chest drain after pleurodesis on volume of drainage as well as absence of fluid on a chest radiograph. There is a concern that a high volume of ongoing chest tube drainage impairs pleural apposition and pleural symphysis. Early chest tube removal is desirable because the average survival for patients with malignant pleural effusion is short. Earlier chest tube removal with the associated reduction in treatment times could also facilitate earlier return to chemotherapeutic agents.

One randomized trial evaluated the effectiveness of short-term versus longer-term drainage after talc slurry pleurodesis in patients with malignant pleural effusions.[8] Chest drains were removed at either 24 hours or 72 hours after talc slurry pleurodesis and the primary outcome measurement was freedom from pleural effusion recurrence at 1 month follow-up. These investigators performed pleurodesis with 4 g of talc when chest tube drainage was less than 150 mL/d. On average, there were 2 days between the insertion of chest drain and the instillation of sclerosant. The investigators found no difference in outcomes between chest tube removal at 24 hours versus 72 hours and an associated decreased length of stay (4 days in the early chest tube removal group vs 8 days in the other group). Pleural effusion recurrence was seen in 2 of 16 (13%) of the 24-hour group and 4 of 19 (21%) in the 72-hour group.

Another study evaluated the efficacy of short-term chest tube drainage versus standard chest tube drainage with tetracycline pleurodesis.[9] Generally it is recommended that pleurodesis be undertaken when chest tube drainage is less than 150 mL/d. In the standard group, pleurodesis with 1.5 g of tetracycline was performed when there was radiologic evidence of lung reexpansion and drainage volume less than 150 mL/d and chest tubes were removed when drainage was less than 150 mL/d. In the short-term group, tetracycline was instilled when the chest radiograph showed the lung to be expanded (usually at 24 hours) and the chest tube was removed the day following tetracycline instillation. A follow-up chest radiograph was obtained at 30 days to determine the response to sclerotherapy. A positive response was no fluid reaccumulation and nonresponders were defined as those with reaccumulation of greater than 50% of the original volume of fluid or those requiring fluid drainage within 1 month after treatment. Successful pleurodesis was seen in 80% and was the same in both groups. The duration of chest tube drainage was shorter in the study group at 2 days versus 7 days median in the standard group. A shorter duration of hospital stay was again shown without sacrificing the efficacy of pleurodesis.

There seems to be no justification for prolonged chest tube drainage either before or after instillation of sclerosant for pleurodesis. Although most physicians use at least 24 hours of chest tube drainage after pleurodesis to promote pleural symphysis, further delay in chest tube removal does not seem to be justified. Strategies such as rolling the patient after instillation of the sclerosing agent and larger chest tubes also have not been shown to offer any substantial advantages.[10]

Having established that talc seems to be the optimal agent for achieving pleurodesis, the next question is what is the optimal method for performing the procedure: following chest tube insertion with talc slurry instillation in the tube or by direct insufflation at the time of thoracoscopic pleural effusion drainage? Thoracoscopic and chest tube drainage can differ in several aspects, which may affect the efficacy of pleurodesis. The extent of drainage of an effusion before pleurodesis can affect the efficacy of pleurodesis and may vary depending whether this is performed via thoracoscopy or via a thoracostomy at the bedside. The distribution of the sclerosant over the pleural space may likewise differ depending on the method of instillation and may affect the likelihood of successful pleurodesis. The most effective sclerosant talc is

often preferentially used in thoracoscopic pleurodesis and less frequently used in chest tube pleurodesis.

In the Cochrane review of 2 randomized studies of thoracoscopic versus chest tube pleurodesis, which included 112 participants, thoracoscopic pleurodesis was found to be more effective than chest tube pleurodesis, with a relative risk of nonrecurrence of 1.19 (95% CI 1.04–1.36).[6] Another review of 5 randomized studies involving 145 patients compared thoracoscopic and bedside instillation of various sclerosants (tetracycline, bleomycin, talc, or mustine).[6] All but one study used talc as the sclerosant in the thoracoscopic arm. The relative risk of successful pleurodesis favored thoracoscopic instillation, with a relative risk of 1.68 (95% CI 1.35–2.10). This review must be interpreted with some caution secondary to the confounding effect of different sclerosants. There was no difference in the mortality among the participants who received thoracoscopic versus bedside instillation of talc. Data from these analyses suggest that thoracoscopic pleurodesis with talc may be the optimal technique for pleurodesis in patients with malignant pleural effusions.

More recently a prospective randomized trial of thoracoscopy with talc versus tube thoracostomy with talc slurry was published.[11] A total of 242 patients were treated with thoracoscopy and 240 were treated with a chest tube. The primary end point was freedom from pleural effusion recurrence. Only patients who achieved at least 90% initial lung reexpansion after drainage were included in the study. In the chest tube group, drainage occurred for 24 to 36 hours before instillation of the sclerosant and chest tubes were removed when the drainage was less than 150 mL/d. Of all patients evaluated, more than 90% lung reexpansion was achieved in 68% of patients treated with chest tubes and 73% of patients treated with thoracoscopy. Thirty-day mortality was high, at 20% in the patients treated with chest tube and 14% in the patients treated with thoracoscopy. Postprocedural respiratory failure and death was seen in 4% of patients treated with chest tube and 8% of patients undergoing thoracoscopy in this study. Overall 30-day successful outcome was not statistically significantly different between the 2 groups, at 78% with thoracoscopy and 71% with chest tube talc slurry instillation. The subgroup with primary lung or breast histopathology had a higher success rate with thoracoscopy (82% vs 67% in chest tube group).

Another prospective study, which was nonrandomized, compared outcomes with thoracoscopic talc pleurodesis versus tube thoracoscopy and talc slurry.[12] Patients at high risk for general anesthesia, and those with poor functional status or short life expectancy, were relegated to chest tube drainage, whereas the others were treated with thoracoscopy. Six grams of talc was used in both groups. Ninety-day outcomes were improved in the thoracoscopy group (88.3%) versus the chest tube group (69.9%). Patients with the tube thoracostomy reported a high incidence of pain with the procedure compared with the patients treated with thoracoscopy. Compared with the other study, no acute respiratory failure or early mortality was seen in either group. Overall survival was 7. 7 months, with a lower survival in the patients treated with chest tube (3.9 months) versus the patients treated with thoracoscopy (11.2 months).

Another large study reported outcomes of thoracoscopic talc pleurodesis in 611 patients treated between 1994 and 2003 with a mean follow-up of 319 days.[13] A total of 17.2% of patients died within 30 days of treatment and Karnofsky index (< 50%) and body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 25 kg/m^2 were predictive of an increased mortality. Radiographic improvement was seen in 68.6% and symptomatic improvement in 89.1%

immediately after drainage. Overall there were only 4 cases (0.6%) of empyema and 2 cases (0.3%) of procedurally related respiratory failure.

Although overall thoracoscopic drainage and pleurodesis seems to be the superior approach, the treatment of symptomatic malignant pleural effusions should be individualized by a patient's functional status and anticipated survival as well as the presence or absence of pleural apposition after drainage. Subjecting patients with poor functional status to thoracoscopy may result in procedure-related respiratory insufficiency and death.

An alternative method of palliating malignant pleural effusions involves the use of tunneled pleural catheters, which are left indwelling long-term. This is an option for patients who obtain symptomatic relief from the pleural drainage but do not show complete or near-complete lung expansion after pleural fluid drainage and are therefore not candidates for pleurodesis because pleural apposition is not obtained. Although prolonged pleural catheter drainage is useful in the management of malignant pleural effusion in the setting of incomplete lung reexpansion after drainage, it is also useful as a therapy for recurrent symptomatic malignant pleural effusion after a failed pleurodesis.

The pleurex catheter is a 15.5-French silicone catheter 66 cm long with fenestrations along the proximal 24 cm. On the distal end is a valve that prevents fluid or air from passing in either direction unless the catheter is accessed with a special drainage line. The pleural fluid is drained by inserting the access tip of the drainage line into the valve of the catheter and then draining into vacuum bottles. Insertion can potentially be performed as an outpatient. Seldinger technique is used to insert a wire into the pleural effusion at the anterior axillary line. A 5- to 8-cm chest wall tunnel is made and the catheter is pulled through the tunnel. After dilation of the wire tract, the catheter is fed through a peel-away sheath and into the pleural space. Given that the presence of a malignant pleural effusion usually precludes cure and objectives are palliative, an advantage of indwelling pleural catheters is that they can cause immediate and long-term relief of symptoms and also minimize or avoid hospitalization altogether.

One large study reviewed the outcomes of 250 tunneled pleural catheters placed in 223 patients (19 patients had bilateral catheters and 8 had repeat ipsilateral procedures).[14] Symptom control was complete in 38.8% of patients and partial in 50%. In 10 patients (4%) there was a failure to successfully place the catheter. Following successful catheter placement, no further ipsilateral procedure was required in 90% of cases. The catheters were placed in a procedure room as an outpatient. Catheters were drained 3 times per week at home.

Most patients had lung cancer (37%), breast cancer (20%), or mesothelioma (12%). There was no difference in symptom control based on primary tumor type. The size of residual effusion at 2 weeks after catheter placement significantly corresponded with the degree of symptom control.

A total of 46% of catheters stayed in until the time of patient death and overall median survival was 144 days. Thirty-day and 1-year mortality were 13% and 84%, respectively. Spontaneous pleurodesis occurred in 43% of patients, allowing removal of the catheter. The catheter was removed once the volume of drainage was less than 50 mL on 3 sequential drainage attempts and fluid reaccumulation was not detected on chest radiograph. In these patients the median duration of catheter drainage was 56 days. The only factor predicting the likelihood of spontaneous pleurodesis was size of residual pleural effusion at less than 20% of original at 2 weeks after placement of catheter with a 57% rate of spontaneous pleurodesis (vs a 25% rate in patients with larger residual effusions).

Although 90% of patients required no reinterventions, 10% required reintervention: repeat catheter placement in 9 patients; thoracentesis in 6 patients; chest tube placement in 5 patients; and pleural fibrinolysis in 4 patients. Fifteen catheters were removed for reasons other than spontaneous pleurodesis: empyema in 5 patients; subcutaneous emphysema in 1 patient; accidental dislodgement in 3 patients; and extrapleural placement in 1 patient.

Complications included unsuccessful placement in 4%; symptomatic loculated effusion in 8.4%; asymptomatic loculation in 4%; empyema in 3.2%; subcutaneous air in 2.4%; cellulitis in 1.6%; and accidental dislodgement in 1.6%.

Empyemas were treated with hospitalization with intravenous antibiotics and continuous pleural drainage via pleural catheter with either thrombolysis or additional chest drains used as needed for loculated collections of fluid.

The investigators did speculate that the lack of complete resolution of symptoms was likely due to coincidental factors such as chronic obstructive pulmonary disease, lymphangitic carcinomatosis, and malignant airway obstruction.

Another study looked at effectiveness of pleural catheter drainage in a subset of patients who would be considered good candidates for pleurodesis.[15] These patients had an estimated survival greater than 90 days and less than 20% residual pleural effusion after drainage (not a trapped lung). Symptomatic improvement was seen in all patients (67% complete and 33% partial). Spontaneous pleurodesis occurred in 76 of 109 patients (70%) at a mean of 90 days. Of the remaining patients, catheters stayed in until death in 19%. Three patients developed empyema (4.6%).

Another study compared the effectiveness of chronic indwelling catheter versus doxycycline instillation via tube thoracostomy in patients with symptomatic malignant pleural effusion.[16] Six of 28 patients (21%) treated with doxycycline pleurodesis had recurrence of the pleural fluid. Twelve of 91 patients with an indwelling catheter (13%) had recurrence of fluid or blockage of the catheter. Symptomatic control after treatment was identical in both groups. A total of 46% of the 91 pleural catheters achieved spontaneous pleurodesis at a median of 27 days. Hospitalization was 1 day for the catheter group and 6.5 days for the doxycycline group. Degree of pain experienced in the 2 groups was similar and overall survival was poor, but similar in both groups (90 days in the patients treated with chest tube and 87 days in the patients treated with pleural catheter). The investigators concluded that a chronic indwelling catheter is an effective treatment option for the management of patients with symptomatic recurrent malignant pleural effusion, and is associated with a shorter hospitalization and the option for outpatient management.

Although long-term pleural catheter placement should be considered the treatment of choice for management of symptomatic malignant pleural effusion in patients with an entrapped lung, controversy remains as to the role in patients thought to be appropriate candidates for standard pleurodesis procedures. Factors influencing this decision may include patient preference, outpatient support for intermittent home drainage, and local institutional expertise.

There are no randomized trials on the role of pleurectomy or decortication in the management of malignant pleural effusions. A review of 5 case series covering 260 patients revealed a perioperative mortality up to 12.5% and a high incidence of prolonged postoperative air leak, at 10% to 20%.[10] This review included patients with mesothelioma and patients with other malignant diseases in which tumor debulking and decortication were part of the procedure. In some patients, decortication was performed when the lung was seen to be entrapped. Except for select patients with a primary pleural tumor (such as mesothelioma) in whom local chemotherapy may be applied, or in cases of indolent metastatic tumors confined to the thorax such as

thymic tumors, this aggressive surgical approach should not be considered. In the general group of patients with metastatic cancer and symptomatic malignant pleural effusions who are debilitated with limited life expectancy, pleurectomy and decortication are generally not recommended given the significant associated major morbidity and mortality.

PLEURAL SPACE INFECTION

Infection of the pleura and pleural space is most often the result of an infection arising in the ipsilateral lung (pneumonia, lung abscess, or bronchiectasis). However, the associated pulmonary consolidation may be minimal. Despite the widespread use of antibiotics for respiratory tract infections, pleural empyema still occurs. At least 40% of all patients hospitalized with pneumonia have an associated pleural effusion.[17] In the United States, empyema is seen in about 60,000 patients annually, with a mortality of 15%.[17] Other causes of pleural sepsis are after lung surgery, trauma, esophageal perforation, and transdiaphragmatic spread of intraabdominal infection. Of all patients with pneumonia who develop a pleural effusion, only a few require intervention for a complicated parapneumonic effusion or an empyema. A parapneumonic effusion refers to any effusion secondary to pneumonia or a lung abscess. An empyema refers to frank pus in the pleural space. Complex parapneumonic effusions and empyema are more common at the extremes of age.

The development of a parapneumonic effusion occurs in 3 clinically relevant stages that represent a continuous spectrum. When the pleura is faced with an infectious organism, it responds with edema and exudation of proteins and neutrophils and a rapid influx of fluid into the pleural space. This process translates in to the classically observed exudative pleural effusion. In the exudative stage the increased rate of pleural fluid formation results from increased permeability of pleural capillaries and the pleural mesothelium. Mesothelial cells play a pivotal role in the development of the intrapleural inflammatory cascade by acting as phagocytes and triggering an inflammatory response when activated by bacteria. The resultant release of chemokines, cytokines, oxidants, and proteases contributes directly to the inflammation as well as secondarily by recruiting neutrophils and mononuclear phagocytes to the pleural space.[17]

The exudative stage is characterized by a sterile exudate secondary to increased permeability of the visceral pleura. The rapidity and extent of progression depends on the type and virulence of the organism, the patient's host defenses, and the timing and effectiveness of antibiotic treatment.[17] Initially, in the uncomplicated parapneumonic effusion, the pleural fluid has a pH greater than 7.20, glucose levels in the normal range and LDH levels less than 3 times the upper limit of normal. Most patients with uncomplicated parapneumonic effusions respond to antibiotics alone. If the infectious injury is promptly resolved, healing typically occurs with few permanent sequelae.

Untreated exudative effusions may develop into fibrinopurulent effusions or complex parapneumonic effusions. The fibrinopurulent stage represents pleural infection with the deposition of fibrin on visceral and parietal pleural membranes and the formation of loculations. Ongoing phagocytosis and cell lysis result in pleural fluid that has a pH less than 7.20, LDH levels more than 3 times normal, and low glucose. Characteristic of the fibrinopurulent stage of pleural sepsis is a disturbance in the physiologic equilibrium between clotting and fibrinolysis within the pleural space. Deposition of fibrin along pleural membranes may occlude lymphatic stomata, thereby decreasing the reabsorption capacity of the pleural space for fluid causing a further

increase in the pleural effusion. Pleural surfaces become coated with fibrin and fibrin strands, which results in adhesions and loculations within the pleural space. This process complicates pleural fluid drainage by preventing the free flow of pleural fluid.[17] This second stage is characterized by a positive Gram stain and/or positive microbial cultures. A complicated parapneumonic effusion requires at least pleural catheter drainage and possibly surgical intervention.

A complex parapneumonic effusion progresses to a pleural empyema when the concentration of leukocytes becomes sufficient to form frank pus as characterized by viscous, whitish-yellow turbid to opaque pleural fluid. Empyema fluid consists of fibrin, cellular debris, and viable or dead bacteria.

The third and final stage of pleural infection is the organizing phase. The organization stage occurs with the influx of fibroblasts into the pleural space and formation of inelastic pleural peel with dense fibrous septations. Fibroblasts grow into the pleural space from both the visceral and parietal pleura. During this fibrotic response the pleural space may become focally or massively obliterated and be accompanied by the formation of dense fibrous adhesions. This process eventually results in a thick pleural peel that restricts chest mechanics and often necessitates a surgical decortication to address restrictive impairment.[17] Animal research suggests an important role for transforming growth factor β in the development of pleural fibrosis.[18]

Presentation of patients with empyema may vary depending on the underlying bacterial cause. Patients with aerobic infections tend to be more acutely ill and the presentation is similar to pneumonia, followed by a nonresolving pneumonia picture with pleuritic chest pain, persistent fever spikes, and failure to improve on appropriate antibiotic therapy. Elderly individuals, immunocompromised patients, and those with anaerobic infections can have a more indolent course and may present with weight loss, cough, fever, and anemia.[19] The pleural effusions are generally evident on chest radiographs. Lateral decubitus films may help to assess loculations. Ultrasound can show the presence of loculations and can also be used to guide pleural drainage, particularly in loculated effusions.[20] CAT scan is helpful to best delineate the size and location of pleural collections, the presence of loculations, as well as the status of the underlying lung parenchyma.[21]

Initial antibiotic coverage of patients with parapneumonic effusions is generally dictated by treatment guidelines for pneumonia and altered according to blood and pleural fluid microbial cultures and sensitivities. Empiric anaerobic antibiotic coverage may be advised because there may be an anaerobic infection, which is generally not so amenable to cultures as anaerobes. Patients with nosocomial empyema need adequate gram-negative coverage. Vancomycin may be added for suspected methicillin-resistant infection. Reported bacteriology of pleural sepsis varies significantly between community acquired and nosocomial infections.[22] Early appropriate antibiotic therapy represents the cornerstone of therapy for pneumonia and parapneumonic effusion.

Minimal size free-flowing effusions may be observed without a diagnostic aspiration because the risk of a complicated course is remote. However, all but the very small free-flowing effusions should be aspirated for diagnostic purposes. Pleural fluid should be evaluated for cytology, cell count, Gram stain, and culture as well as pH, LDH, glucose, and protein.

Uncomplicated parapneumonic exudative effusions that are of small volume and free flowing without loculations with a negative Gram stain, pH greater than 7.20, and negative cultures are usually inflammatory in nature and have no detectable bacterial pathogens. Most of these resolve with antibiotic therapy for the underlying pneumonia and can therefore be observed without formal drainage.[17]

However, early drainage of pleural fluid becomes necessary when a parapneumonic effusion advances beyond the exudative stage to the fibrinopurulent stage and becomes a complicated parapneumonic effusion. Indications for immediate drainage are large effusions (>half the hemithorax), effusions with loculations, pH less than 7.20, positive Gram stain or culture and low glucose levels. The presence of frank pus on aspiration, which constitutes an empyema, is also an indication for immediate drainage.[17]

Options for drainage include: multiple thoracenteses; tube thoracostomy (± intrapleural fibrinolytics); thoracoscopic drainage; thoracotomy and drainage (± decortication); and chronic open drainage. Choice of drainage is dependent on the viscosity of the pleural fluid, location, volume and extent of loculations, and the general condition of the patient.

Multiple thoracenteses are generally not recommended. One study showed patients required an average of 7.7 aspirates and had a hospital stay of 31 days.[23]

Tube thoracostomy is generally performed with a size 24 to 28 French chest tube placed in a dependent area (usually the posterior costophrenic recess). Sometimes ultrasound guidance can be used to guide placement of smaller tubes. The benefit of image guidance for smaller tubes may be offset by the greater propensity of the smaller tubes to clot.

Complicated parapneumonic effusions and empyema are characterized by a procoagulant state within the pleural space, which results in the progressive development of dense layers of fibrin and loculations, as discussed earlier. These complex loculated effusions may not be adequately drained with a simple tube thoracostomy alone. Options for treatment include tube thoracostomy with subsequent administration of fibrinolytic agents thorough the tube, or surgical thoracoscopic drainage with mechanical disruption of adhesions and complete evacuation of thick inflammatory debris.

One could theorize that the administration of intrapleural fibrinolytics early in the fibrinopurulent phase could prevent loculations and promote pleural drainage. Intrapleural instillation of fibrinolytic agents theoretically could dissolve fibrinous clots and adhesions and prevent pleural loculations. The hope of intrapleural fibrinolytics would be to enhance pleural fluid drainage via tube thoracostomy and reduce the need for thoracoscopic surgical drainage. Use of fibrinolytic agents is appealing because the most common reason for failure of pleural drainage among patients with an appropriately positioned catheter is occlusion of the catheter by viscous fibrin-rich fluid and cellular debris, or the formation of fibrin strands that form pleural loculations that sequester pleural fluid and prevent it from reaching the chest tube. Side effects are minimal with rare reports of fever and bleeding.[24]

Streptokinase, urokinase, and tissue plasminogen activator are 3 fibrinolytic agents that have been widely used via chest tube instillation in the treatment of loculated parapneumonic effusion and empyema. Streptokinase is usually administered as 250,000 IU in 100 to 200 mL saline daily for up to 7 days. Urokinase is usually administered as 100,000 IU in 100 mL saline daily up to 3 days. Tissue plasminogen activator is usually administered as 10 to 25 mg twice daily up to 3 days. Drains should be clamped for 2 to 8 hours following the administration of the fibrinolytic. Tissue plasminogen activator provides fibrinolytic activity without the antigenicity of streptokinase.[17]

Tuncozgur and colleagues[25] looked at fibrinolytic versus saline instillation via chest tube in 49 patients. They found a significantly lower decortication rate (60% vs 29%) and shorter duration of hospitalization (14 vs 21 days) with the addition of intrapleural fibrinolysis as well as a greater volume of chest tube drainage (1.8 L vs 0.8 L).

A single-center randomized placebo-controlled study by Diacon and colleagues[26] reported that intrapleural streptokinase resulted in faster resolution of infection and reduced need for surgery (13.6% vs 45.5%) and improved outcomes in patients with complex parapneumonic effusions and empyema.

Another prospective study by Misthos and colleagues[27] investigated tube thoracostomy versus tube thoracostomy and streptokinase. Tube thoracostomy alone was successful in 67% of cases. Instillation of streptokinase led to a favorable outcome in 87% and significantly shortened hospital stay, mortality, and rate of surgical intervention.

Davies and colleagues[28] compared fibrinolysis versus saline control in the second to fifth hospital day in 24 patients with tube thoracostomy for empyema. These investigators looked at volume of drainage and improvement in chest radiographs. Fibrinolytics caused an increased rate of fluid drainage and greater improvement on chest radiograph. No bleeding complications were seen. Three patients in the control group and none in the fibrinolytic group required surgical drainage.

Bouros and colleagues[29] compared fibrinolytics with saline control in 31 patients. Fibrinolytic patients had a larger volume of drainage and higher rates of successful chest tube drainage (87% vs 25%) compared with saline control patients. Two patients treated with fibrinolytic therapy required surgical drainage and 12 patients with saline crossed over to fibrinolytic therapy, with 6 of 12 ultimately requiring surgical drainage.

Tokuda and colleagues[30] published a meta-analysis of all the major placebo-controlled studies on intrapleural fibrinolysis, and although they showed a trend toward improved survival and a decreased need for surgical interventions, the differences failed to be statistically significant.

Twenty-five small uncontrolled clinical trials reported on the safety and efficacy of intrapleural fibrinolytics in decreasing the need for surgical intervention. Aggregate mean success rate in avoiding surgery was 82% for streptokinase and 84% for urokinase. When treatment failure was considered as surgical intervention, fibrinolytics decreased the risk of this outcome (relative risk 0.63; 0.46–0.85).[31] However, there was discordance between the early studies and the more recent randomized control study by Maskell reported later.

The largest prospective multicenter double-blind controlled MIST trial (Multicenter Intrapleural Sepsis Trial) on the role of intrapleural streptokinase for pleural infection was reported in 2005.[32] In this large trial multicenter patients received either streptokinase (250,000 IU twice daily for 3 days) via chest tube or saline placebo. Primary end points of the study were death and need for surgical drainage. A total of 454 patients with pleural pus, pH less than 7.20, or bacterial invasion of the pleural space were randomized to chest tube drainage or tube drainage and streptokinase. The proportion of patients who died or needed surgery at 3 months was similar between streptokinase and control (31% vs 27%, $P = .43$). No differences in mortality, rate of surgery, radiographic outcomes, or length of hospital stay were shown. This study did not substantiate the role of streptokinase in pleural infections. The investigators speculated that the increased viscosity of pleural pus in patients with empyema may be related to high concentrations of DNA resulting from breakdown of phagocytes, bacteria, and other intrapleural cells and that DNase in addition to fibrinolytics may be more effective than fibrinolytics alone.

Antibiotics alone remain the standard for uncomplicated parapneumonic effusions. For free-flowing complicated parapneumonic effusion or unilocular empyema, tube thoracostomy or percutaneous catheter drainage remain the standard of care. No high-grade evidence from a large-scale randomized controlled study exists to support

the administration of fibrinolytic therapy and so it should not be routinely used for all such patients. However, critics have pointed out that the duration of therapy and other methodologic issues in the randomized trial may have contributed to the failure of lytic therapy to show a significant advantage. In many centers lytic therapy is the mainstay of management for early empyema and substantially reduces the burden of patients needing surgical decortication.

Surgical drainage via thoracoscopy is the optimal therapy in patients who fail chest tube drainage, such as patients with an organized empyema with highly viscous pleural fluid and a trapped lung who experience failure of a tube thoracostomy to yield reexpansion of the lung.

Surgical therapy is also optimal primary therapy in patients who present with multilocular complex parapneumonic effusions and empyema. However, there does seem to be a place for selective use of fibrinolytics in the early management of patients who fail drainage with appropriate sized chest tubes if reasons exist to avoid definitive surgical drainage. Fibrinolytic therapy may therefore be considered in poor surgical candidates who fail chest tube drainage, or in those who require a period of medical stabilization before surgery is performed, as well as in centers where surgical facilities are limited. Patient factors, local expertise, and surgical availability to a certain extent dictate the initial choice between tube thoracoscopy and fibrinolytics or thoracoscopy. Surgical drainage via thoracoscopy may be performed following fibrinolytics if complete drainage is not achieved.

As noted earlier, thoracoscopy seems to be the optimal treatment option for patients with an incompletely drained thick unilocular collection with incomplete lung expansion, as well as in patients with multiloculated parapneumonic effusion and empyema because loculations can be broken down, thick pleural fluid and debris completely evacuated, the pleural space can be extensively lavaged, and chest tubes can be carefully placed. However, the alternative to early surgical drainage via thoracoscopy is tube thoracostomy in all patients ($\pm$ fibrinolytic therapy) and reserving surgery for those patients who cannot be managed by nonsurgical means.

Several small retrospective and unblinded prospective studies suggest that thoracoscopy is superior to tube thoracostomy with fibrinolytics, with the need for thoracotomy halved.[33–35] In the only prospective randomized controlled trial of fibrinolytic therapy versus thoracoscopy for empyema, Wait and coworkers[36] randomly assigned 20 patients with complicated multiloculated parapneumonic and empyema to streptokinase (250,000 IU daily for 3 days) via tube thoracostomy or immediate thoracoscopic drainage. Thoracoscopy had a higher treatment success rate (91% vs 44%), lower duration of chest tube drainage (5.8 vs 9.8 days), and a shorter hospital stay (8.7 vs 12.8 days). This study supports the preferred approach of primary thoracoscopic drainage in patients presenting with multilocular collections, provided that they are suitable candidates for surgical intervention.

Decortication is a procedure in the chronic organizing phase that aims to restore chest mechanics by removing a restrictive fibrotic peel when the underlying lung is unable to expand (ie, trapped lung) because of the establishment of a thick inflammatory coat. The procedure entails the excision of all the fibrous tissue from the pleura to permit lung reexpansion.[37] Decortication relies on lung elasticity to fill the cavity. Lung constriction after empyema can reduce lung perfusion by 20% to 25% on the involved side. If after 6 months the pleura remains thickened and the patient's pulmonary function is sufficiently reduced to limit activities, decortication should be considered. The pulmonary function of patients who undergo decortication can increase significantly. Decortication can improve lung perfusion and improve vital capacity from 62% up to 80% and the FEV_1 (forced expiratory volume after 1 second) from 50% to 69%.

Despite the improvement in volumes, the affected lung still remains impaired. It remains a procedure with significant morbidity and a reported mortality of up to 10% so the patient must be fit enough for a major intervention.[35] Some investigators report that pleural thickening may resolve over time and recommend deferring decortication for up to 6 months.[38] For asymptomatic patients in whom the sepsis has cleared, the benefit of the procedure is not proved and observation is warranted.

When managing patients with pleural infections in the acute stage, decortication should be considered only for control of pleural sepsis and is rarely required. Generally in the acute phase, lung expansion is possible with thoracoscopic drainage because pleural encasement is not fibrotic. Failure of reexpansion of the lung in the acute phase may be more often secondary to problems of the underlying lung parenchyma that would not be responsive to pleurectomy. It should be applied in the acute phase only if the pleural sepsis cannot be controlled in any other way; debilitated patients may be better managed with open thoracosotomy.

For patients in whom sepsis cannot be controlled acutely with thoracoscopic drainage, and in whom decortication is not appropriate, then window thoracostomy may be performed. Open thoracostomy may be the procedure of choice if there is a permanent supply of causative organisms as a result of bronchopleural fistula or if there is a space issue such as in a postpneumonectomy empyema. Postpneumonectomy empyema is a result of bronchopleural fistula in 80% to 100% of cases, with a mortality of 5% to 35%.[39,40] From 2% to 10% of pneumonectomies are followed by the development of a bronchopleural fistula.[39]

Open thoracostomy may be performed as a permanent procedure, or as a preliminary procedure before a more definitive treatment.

Definitive treatment after open thoracostomy is a procedure for obliterating the pleural space and this can be accomplished by one of 2 approaches. Thoracoplasty entails diminishing the distance between the lung parenchyma and chest wall by collapsing the roof of the chest wall.[41] The other option is to fill the space with transposition of viable tissue such as omentum or skeletal muscle. It can be performed as a primary procedure to manage an empyema space or as a staged procedure some months after an open thoracostomy. If an empyema is associated with a bronchopleural fistula, that also needs to be addressed. Operative closure of the bronchial stump can be performed via the previous thoracotomy or transsternally using a transpericardial approach.[42] Amputation of the airway stump and, on occasion, even carinal resections have been reported.[43] For chronic leaks from the peripheral lung (not the central airway) caused by destruction of the barrier function of the pleural space, placement of vascularized tissue and pleural space obliteration alone should be adequate.

SUMMARY

Pleural effusions can occur because of a host of underlying problems. Initial evaluation includes taking a careful medical history, performing a thoracentesis and pleural fluid analysis, and CAT scan imaging. If the cause of the effusion is still not clear after these evaluations and the effusion persists, then a thoracoscopic evaluation with pleural biopsy is generally indicated.

Malignant pleural effusions are ideally treated with thoracoscopy and talc pleurodesis. In patients with poor functional status, tube thoracoscopy and subsequent pleurodesis with sclerosant instillation via the chest tube may be better tolerated. Patients with an entrapped lung are optimally treated with a semipermanent indwelling pleural catheter.

Patients with pneumonia and associated pleural effusion should also be evaluated with thoracentesis. Presence of loculations, or pleural fluid analysis showing bacteria

on Gram stain or culture, low glucose or low pH, and frank pus are all indications for immediate drainage. Nonloculated parapneumonic effusion and empyema may be adequately treated with a tube thoracoscopy, but loculated effusions, or those inadequately drained with a chest tube, are best treated with thoracoscopic drainage or a trial of lytic therapy. The fundamental principle of therapy is to eliminate residual space between the pleural surfaces. Existence or lack of dead space within the pleural cavity is a decisive factor influencing outcomes because no effective infection control can be expected in the presence of an active cavity. In select symptomatic patients who have persistent lung entrapment after treatment of an empyema with an associated restrictive defect, thoracotomy and decortication may be indicated to improve pulmonary function.

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