Review Article on Interventional Pulmonology in the Intensive Care Unit

Management of complex pleural disease in the critically ill patient

Kurt Hu[1], Amit Chopra[2], Jonathan Kurman[1], J. Terrill Huggins[3]

[1]Division of Pulmonary and Critical Care Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [2]Division of Pulmonary and Critical Care Medicine, Albany Medical College, Albany, NY, USA; [3]Division of Pulmonary, Critical Care, and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kurt Hu. Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. Email: kuhu@mcw.edu.

Abstract: Disorders of the pleural space are quite common in the critically ill patient. They are generally associated with the underlying illness. It is sometimes difficult to assess for pleural space disorders in the ICU given the instability of some patients. Although the portable chest X-ray remains the primary modality of diagnosis for pleural disorders in the ICU. It can be nonspecific and may miss subtle findings. Ultrasound has become a useful tool to the bedside clinician to aid in diagnosis and management of pleural disease. The majority of pleural space disorders resolve as the patient's illness improves. There remain a few pleural processes that need specific therapies. While uncomplicated parapneumonic effusions do not have their own treatments. Those that progress to become a complex infected pleural space can have its individual complexity in therapy. Chest tube drainage remains the cornerstone in therapy. The use of intrapleural fibrinolytics has decreased the need for surgical referral. A large hemothorax or pneumothorax in patients admitted to the ICU represent medical emergencies and require emergent action. In this review we focus on the management of commonly encountered complex pleural space disorders in critically ill patients such as complicated pleural space infections, hemothoraces and pneumothoraces.

Keywords: Pleural disease; empyema; pneumothorax; hemothorax; pleural effusion of extra vascular origin; criticall illness

Submitted Mar 01, 2021. Accepted for publication Jun 21, 2021.
doi: 10.21037/jtd-2021-31
View this article at: https://dx.doi.org/10.21037/jtd-2021-31

Introduction

Pleural disorders are common in the intensive care unit (ICU). While most pleural disorders occur concurrently through the course of the illness, occasionally, pleural disorders can be the primary reason for an ICU admission. Some pleural diseases, such as complicated parapneumonic effusions (CPEs), hemothorax, and pneumothorax, can often be challenging to manage and may require expert consultation. In this manuscript, we will review the management of complex pleural space infections, hemothorax, and pneumothorax in the critically ill patient.

Infected pleural space

An infected pleural space can be further classified into simple parapneumonic effusions, CPE, empyema, infected bronchopleural fistula, and empyema necessitans. These can be seen in the setting of pneumonia, hematogenous spread, penetrating trauma, or as a result of surgery.

Definition

Parapneumonic effusions result from pneumonia, lung abscess, or bronchiectasis (1). While CPE is defined by

Table 1 Characteristic findings of the spectrum of parapneumonic effusions

Characteristics	Uncomplicated parapneumonic effusion	Complicated parapneumonic effusion	Empyema
Appearance	Turbid	Cloudy	Purulent
pH	>7.30	<7.20	NA
Glucose level, mg/dL	>60	<60	NA
LDH, U/L	<700	>1000	NA
Gram stain	Negative	May be positive	Positive

LDH, lactic acid dehydrogenase; NA, not applicable.

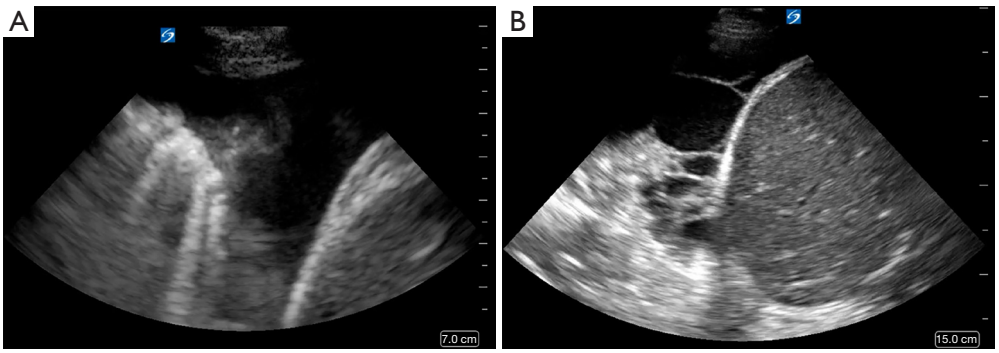

Figure 1 (A) Simple appearance on ultrasound evaluation. This requires diagnostic thoracentesis (*Video 1*). (B) Complex appearance on ultrasound evaluation. This requires chest tube drainage (*Video 2*).

the criteria as outlined in *Table 1*. An empyema is a severe form of CPE defined by the presence of pus in the pleural space. Some would suggest that an empyema may also be defined with a positive gram stain or culture; however, we reserve the true definition of empyema as the presence of purulent fluid (2). Empyema necessitans is a complication of poorly controlled empyema resulting in the infection eroding through the parietal pleura into the soft tissue and ultimately the skin.

Pathophysiology

Infection of the pleural space develops when a pathogenic organism seeds this area. While pneumonia is the leading cause of empyema, it can occur from direct inoculation (e.g., trauma), other surrounding sources (e.g., esophageal perforation, mediastinitis, subdiaphragmatic abscess), or bacterial seeding from preexisting effusion (3). In this review, we will focus primarily on the treatment of CPE/empyema as they are the most common community acquired or nosocomial pleural infections acquired by critically ill patients (4,5).

Parapneumonic effusions are categorized into three loosely defined stages: (I) simple or uncomplicated parapneumonic/exudative (stage I); (II) CPE/empyema/fibrinopurulent (stage II); and (III) organizing (stage III) (6). These stages exist along a continuum of an evolving process. An uncomplicated parapneumonic effusion refers to free-flowing effusions that are sterile. On pleural ultrasound, these effusions appear anechoic and lack complexity (7). A CPE refers to an effusion that has been infected with bacteria or other micro-organisms with a pleural fluid analysis demonstrating intense pleural space inflammation and/or positive gram stain. Pleural ultrasound will typically show septations demonstrating complexity in the pleural space (7). An empyema refers to a collection of pus. Pleural ultrasound for empyema may show a homogenously complex pleural effusion or complex septated (7) (*Figure 1A,1B*).

The pathogenesis of a stage I uncomplicated parapneumonic effusion results from capillary leak mechanisms resulting in the movement of fluid into the pleural space. With progression to stage II, direct bacterial invasion into the pleural space enhancing the formation of

septae and increased pleural fluid viscosity. During stage III, progressive fibrin deposition and adhesions from on the visceral pleura surface and pleural space which may lead to a mature fibroelastic membrane which will impede the lung from full re-expansion with fluid evacuation.

Clinical presentation

The clinical presentation of a pleural infection is often hard to distinguish in patients who have a lower respiratory tract infection. However, a few features may increase the probability that a parapneumonic effusion has developed. These findings include the following: (I) pleurisy; (II) lack of improvement or clinically worsening despite appropriate antimicrobial coverage; and (III) radiographic studies that may demonstrate an increasing effusion. All patients with pneumonia should be promptly evaluated for the presence of a parapneumonic effusion, sampled, drained, and submitted for proper pleural fluid analysis and microbiologic studies that are properly inoculated into aerobic and anaerobic blood culture bottles.

Diagnosis

The diagnosis is made by thoracentesis. Although 90% are simple and do not require drainage, early identification and treatment is vital to prevent further progression and complications (8). CPE is diagnosed by the pleural fluid analysis, while empyema occurs when the presence of purulence is noted on fluid appearance. All patients with pneumonia with an effusion should be evaluated for parapneumonic effusion. *Table 1* summarizes the pleural fluid characteristics of uncomplicated parapneumonic effusion, CPE, and empyema.

The diagnosis of pleural infection can be a challenging task in the ICU setting. The portable chest radiograph (CXR) is the most commonly utilized imaging study to evaluate pleural effusions among critically ill patients. CXR findings are nonspecific and needs 175–525 mL of fluid accumulation before distinguishing the presence of a pleural effusion (9). Even when multiple X-ray views are available, a plain radiograph can miss up to 10% of patients with pleural infections (10).

Thoracic ultrasound (TUS) has become ubiquitous in many ICUs and has the unique capability to identify a pleural effusion. In turn, this can aid with prediction of CPE and establish prognosis (7,11). TUS can facilitate timely administration of help in initiating early therapy, such as intrapleural fibrinolytics (12-14) (*Figure 1A*,*1B*). While computed tomography (CT) can diagnose underlying pneumonia, it is less useful in characterizing septations and other pleural space pathology or help to plan for safe entry into the pleural space. The transportation of unstable, critically ill patients may not be justifiable for the information obtained. CT scan has a role in patients who are not responding to therapy to identify alternate diagnosis or loculated pleural space not seen by TUS, such as fluid accumulation posterior to the scapulae or a mediastinal pocket.

Management

The principle of management of the infected pleural space is governed by early antibiotics and early evacuation of pleural fluid in the setting of a CPE and/or empyema.

Antimicrobial

Typically, empyema mimics the underlying pneumonia. Community-acquired infections are generally caused by streptococcus and staphylococcus species (15). In nosocomial infections, MRSA and gram-negative bacteria should be considered for initial antimicrobial therapy. The identification of causative organisms from blood, pleural fluid, and pleural biopsy occurs in 10%, 20%, 45% of cases, respectively (16). In up to 76% of cases, anaerobes may be present but not isolated by standard means (17,18). Therefore, empiric antibiotics should not only aim at covering typical organisms based on local antibiograms but also target anaerobic bacteria (19-22). Most antibiotics for pneumonia penetrate well into the pleural space. However, the acidic environment inactivates aminoglycosides and should be avoided (23). *Table 2* summarizes the most common organisms in empyema.

The duration of antibiotic therapy needs to be individualized. Antibiotic therapy should be continued until there is both clinical and radiographical improvement. Therapy may need to be prolonged even after adequate drainage, and a course of 4–6 weeks is recommended (24).

Tube drainage

The goal of tube drainage is to resolve sepsis and prevent lung entrapment and long-term consequences of fibrothorax or trapped lung. Therefore, early control of pleural infection is vital. Treatment may begin with antibiotics, but ultimately rapid pleural drainage is necessary to prevent progression to the fibrosing and organizing stage of an

Table 2 Common bacteria organisms that cause complex parapneumonic effusion or empyema

Common organisms found in complex parapneumonic effusions/empyema
Gram positives
Streptococcus pneumoniae
Streptococcus pyogenes
Staphylococcus spp.
Gram negatives
Klebsiella pneumoniae
Enterobacteriaceae spp.
Pseudomonas aeruginosa
Anaerobes
Fusobacterium nucleatum
Streptococcus milleri group (*intermedius, constellatus, mitis*)
Prevotella spp.
Bacteroides spp.
Peptostreptococcus spp.

The most common community-acquired pathogens are *Streptococcus pneumoniae*. The most common healthcare-associated pathogens are MRSA and gram-negative bacteria. Up to 76% of anaerobes are not present on culture but can be found on genetic sequencing.

empyema.

Although there seems to be no debate among providers for the necessity of drainage, the ideal size of the chest tube remains in contention. Some experts maintain that small-bore catheter may be inadequate when loculation and frank purulence is present (25). However, this has not been demonstrated by randomized control trials. *Table 3* summarizes the failure rate of pleural drainage and the chest tube bore size placed in numerous studies. Small-bore chest tubes (≤14 Fr) improve patient comfort and avoid complications associated with large-bore chest tubes while still having similar success rates (1,27,37). Placement by Seldinger technique under ultrasound (US) allows for accurate insertion of the chest tube into the dominant pocket of a loculated effusion.

Blunt dissection insertion technique still has some advantages. At times, especially in patients with thick chest walls, it may be challenging to pass the introducer needle into the pleural space. Seldinger technique should ideally be performed with US localization in the interest of patient safety (38). When US availability is limited, and imaging is inadequate for clear guidance, tactile feedback with physical guidance of the pleural tube along the lung tissue may be substituted. *Figure 2* shows the confirmation of the guidewire in the pleural space during insertion of a chest tube using Seldinger technique.

Intrapleural fibrinolytic therapy (IPFT)

IPFT has been part of the treatment algorithm for pleural empyema for more than half a century. It was first described by Tillett in 1949. Tillett and colleagues described the combination of streptokinase and streptococcal deoxyribonuclease to decrease the pleural fluid viscosity and improved drainage of patients with empyema (39). Since then, there have been numerous smaller randomized control trials that have resulted in promising data, which have reduced the requirement for surgical intervention (33-36).

The Multicenter Intrapleural Sepsis Trial (MIST) was unable to find any difference in drainage failure between using fibrinolytic alone versus placebo (19). The second intrapleural sepsis trial (MIST2) added dornase alfa (DNAse) to fibrinolytics (39). The authors compared alteplase (tPA) alone, DNAse alone, tPA and DNAse, and placebo. They recruited 210 subjects, the majority of whom had small-bore chest tubes (<15 Fr). The primary outcome of MIST-2 was based on radiographic change on CXR. The results of the study found no difference

Table 3 Summary of major trials with outcomes and chest tube size

Trial	Chest tube size	CPE (N)	IPFT use	Failure type/rate
Trials where no IPFT was used				
Keeling *et al.* (26) 2008	8–12 Fr	52	UK as needed	Surgical referral 12/52 (19%)
Rahman *et al.* (27) 2010	<10 Fr	58	NS 30 mL q6h	Death and surgery 21/58 (36%)
Rahman *et al.* (27) 2010	10–14 Fr	208	NS 30 mL q6h	Death and surgery 75/208 (36%)
Liang *et al.* (12) 2008	10–14 Fr	59	NR	Mortality 27/59 (46%)
Moulton *et al.* (28) 1995	10–16 Fr	118	UK in 98/118	Surgery or death 7/118 (6%)
Liu *et al.* (13) 2010	10–16 Fr	119	NR	Large bore insertion Surgical referral 33/119 (28%)
Chen *et al.* (14) 2009	12–16 Fr	141	NR	Mortality Surgical referral 52/141 (37%)
Horsley *et al.* (29) 2006	16.2±0.6 Fr	10	NR	Resolution of empyema 8/10 (80%)
Rahman *et al.* (27) 2010	15–20 Fr	70	NR	Death and surgery 28/70 (40%)
Matsunuma *et al.* (30) 2016	<20 Fr	24	NR	Death, reinsertion of CT, or surgery 5/24 (21%)
Matsunuma *et al.* (30) 2016	>20 Fr	27	NR	Death, reinsertion of CT, or surgery 5/27 (19%)
Rahman *et al.* (27) 2010	>20 Fr	69	NR	Death and surgery 30/69 (44%)
Huang *et al.* (31) 1999	24–32 Fr	100	NR	Incomplete drainage, fever, death 47/100 (47%)
Trials where IPFT was used				
MIST1 (19) 2005	12–20 Fr	454	SK *vs.* NS	Surgery or death 74/224 SK group 63/224 NS group 137/454 (30%)
MIST2 (32) 2011	<15 Fr	210	tPA *vs.* tPA + DNAse *vs.* DNAse *vs.* NS	Surgery 3/48 tPA 2/48 tPA + DNase 18/46 DNAse 8/51 NS 31/210 (15%)
Davies *et al.* (33) 1997	14 Fr	24	SK *vs.* NS	Surgical referral 3/12 NS group 0/12 SK group 3/24 (13%)

Table 3 (*continued*)

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Trial	Chest tube size	CPE (N)	IPFT use	Failure type/rate
Diacon *et al.* (34) 2004	24 or 28 Fr	44	SK *vs.* NS	Surgical referral
				3/21 SK group
				10/21 NS group
				13/42 (31%)
Misthos *et al.* (35) 2007	28-32 Fr	127	SK *vs.* NS	Surgery or death
				8/57 SK group
				26/70 NS group
				34/127 (27%)
Bouros *et al.* (36) 1999	28-32 Fr	31	UK *vs.* NS	Surgical referral
				2/15 UK group
				10/16 NS then UK
				12/31 (39%)

CPE, complicated parapneumonic effusion; IPFT, intrapleural fibrinolytic therapy; Fr, French; UK, urokinase; NS, 0.9% saline; NR, not reported; CT, chest tube; SK, streptokinase; tPA, alteplase; DNAse, dornase alfa.

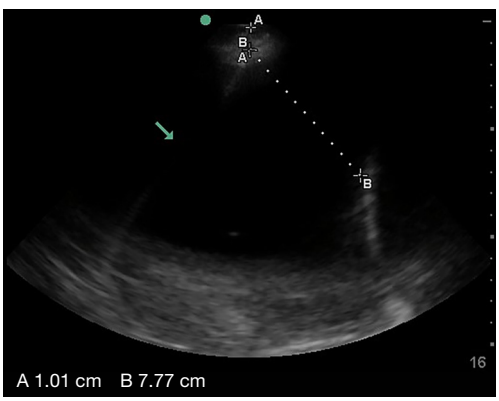

Figure 2 Ultrasound image of confirmed guidewire placement in the pleural space. The green arrow points towards the echogenic wire in the anechoic pleural fluid.

in radiographic change when comparing placebo to tPA or DNAse alone (–17.2% *vs.* –17.2% *vs.* 14.7%; P=0.55, P=0.14). However, when tPA and DNAse were combined, there was a significant decrease in radiographic findings (–29.5% *vs.* –17.2%; P=0.005), surgical referrals (4.1% *vs.* 16%; OR 0.17; P=0.03), and hospital length of stay (11.8±9.4 *vs.* 24.8±56.1 days; P<0.001). Three open-label trials after MIST2 have confirmed the effectiveness of tPA/DNAse combination (40-42). A recent Cochrane review also showed that IPFT reduces surgical referral but does not reduce mortality (43).

MIST2 used a combination of 10 mg of tPA and 5 mg of DNAse instilled into the pleural space 2 hours apart every 12 hours for three days (32). This practice can sometimes be cumbersome and resource-intensive. Majid and colleagues showed that the simultaneous administration of tPA and DNAse did not change the clinical outcome (41). Mehta and colleagues showed that once a day administration of 10 mg of tPA and 5 mg of DNase was adequate for therapy (42). The findings of these open-label trials are summarized in *Table 4*. The ideal dosing and schedule for tPA/DNAse have yet to be determined.

The main complication of IPFT is intrapleural bleeding and has a reported incidence of 1.8–12% (40-42,45). tPA is the primary risk factor for hemorrhage. No ideal dose of tPA or DNAse has been determined. The ADAPT trial showed that decreasing tPA from 10 mg to 5 mg in combination with DNAse did not reduce efficacy (44). The ongoing ADAPT-2 trial may further improve the safety of this treatment by supporting for the additional reduction in tPA dosing. Alternatively, the use of urokinase has been shown to have similar efficacy but with significantly less intrapleural hemorrhage (46).

Table 4 Summary of major open label IPFT trials since MIST2. tPA, alteplase; DNAse, dornase alfa

Study	Intervention	N	Need for surgery (%)	Mortality (%)
MIST 2 trial (32) 2011	10 mg tPA and 5 mg DNAse 2-hour apart q12 hours	48	2 (4.2)	4 (8.3)
Piccolo *et al.* (40) 2014	10 mg tPA and 5 mg DNAse 2-hour apart q12 hours	107	8 (7.5)	3 (2.8)
Majid *et al.* (41) 2016	Concurrent 10 mg tPA with 5 mg DNAse q12 hours	73	7 (9.6)	2 (2.7)
ADAPT trial (44) 2016	Reduced 5 mg tPA with 5 mg DNAse q12 hours	61	3 (4.9)	1 (1.6)
Mehta *et al.* (42) 2016	Daily 10 mg tPA with 5 mg DNAse	55	4 (7.3)	3 (5.5)

Novel techniques

A possible alternative to IPFT is pleural irrigation. A pilot trial of 47 patients compared either flushing 250 mL of 0.9% saline into the pleural space by gravity through a small-bore chest tube or standard therapy. The use of pleural saline irrigation reduced surgical referrals with no significant adverse effects (47).

Additional drainage tubes

When drainage is inadequate from a single chest tube, which may occur with a multiloculated effusion despite IPFT, we recommend that additional catheters be placed under image guidance. CT imaging is preferred but can be done under ultrasound in the hand of experienced providers. Additional IPFT through a second or third drain may provide clearance and avoid surgery. However, the efficacy and safety of this approach remain unclear.

Assessment for improvement

Assessing the efficacy of therapy with drainage volume alone may be falsely reassuring. Traditionally, a CT scan is the best modality for radiographic improvement as it allows for evaluation of the underlying parenchyma and visualization of additional locules (48). However, transporting a critically ill patient has risks (49). TUS can help determine if the fluid around the catheter is adequately drained and can be performed rapidly at the bedside by the clinician.

Medical thoracoscopy (MT)

MT is a minimally invasive procedure that has been around for more than a century. It may be an alternative to surgical decortication. MT has been shown to be safe and effective in the treatment of pleural infections (50-52). MT can be performed by either an interventional pulmonologist or a thoracic surgeon and be conducted with local anesthesia and moderate sedation. A recent small trial comparing IPFT versus MT, showing that MT has the potential to reduce hospital length of stay (53). Although there remains a lack of data, MT should be considered as an alternative to surgery when conservative measures fail.

Surgical options

The perioperative mortality rate for a surgical decortication procedure for pleural infection is reported to be 3.1%, with significant postoperative morbidity of 30.2%. Open thoracotomy carried higher perioperative mortality and postoperative morbidity when compared to video-assisted thoracoscopic surgeries (VATS) (mortality 2.8% *vs.* 3.7%; morbidity 13.9% *vs.* 18.0%). Patients of older age, reduced renal function, elevated BMI, COPD, and decreased functional status were all predictors of mortality and morbidity. Sicker patients with higher American Society of Anesthesiologist (ASA) physiological status classes (ASA I/II *vs.* ASA III/IV/V/VI) were two times as likely to die [OR 2.07 (1.66–2.60), P<0.001] and ten times more likely to have significant morbidity [OR 10.15 (1.41–73.12), P=0.0215] (54). Therefore, all other options should be exhausted before resorting to surgery.

Summary

Early diagnosis of pneumonia and the use of antibiotics has decreased the overall incidence of pleural infections and pleural space complications. However, epidemiological studies suggest that the rates of complicated pleural infections may be rising again (5). Undoubtedly, a subset of these patients will present to the ICU. Early diagnosis and proper antibiotic selection are still the cornerstones of initial therapy. TUS evaluation should be performed on all patients with pneumonia to rule out CPE. Pleural sampling should be used for diagnosis. Pleural drainage is needed for all CPE/empyema. The use of small-bore chest tubes has a similar failure rate compared to large-bore chest tubes and is more comfortable for patients. IPFT should be started

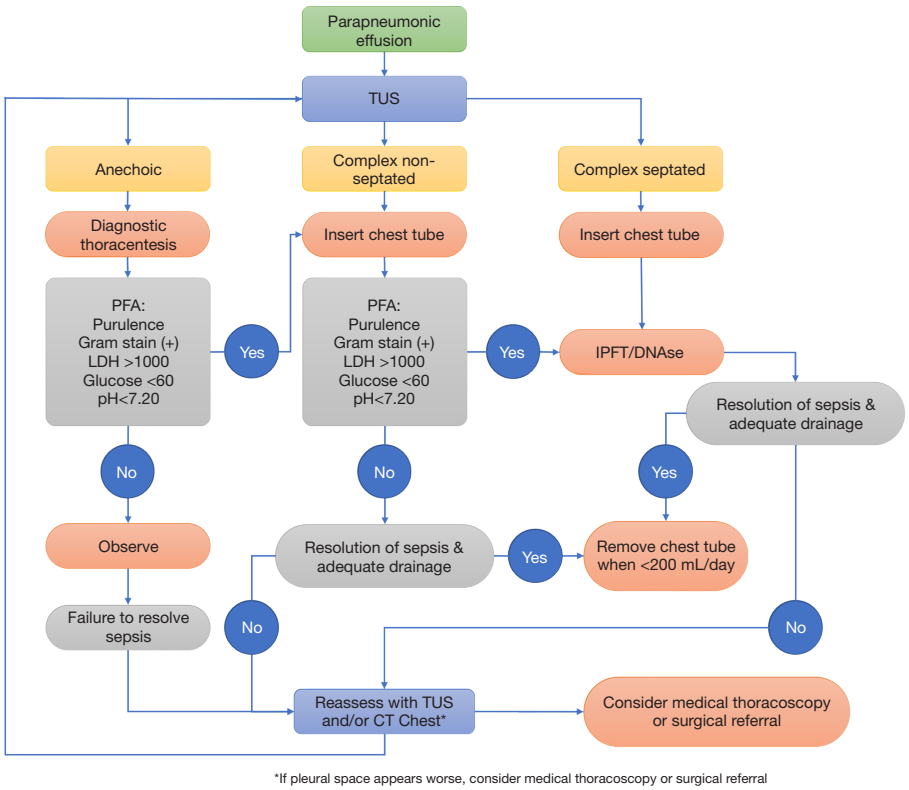

Figure 3 Algorithm for evaluation and management of parapneumonic effusion. TUS, thoracic ultrasound; PFA, pleural fluid analysis; LDH, lactic acid dehydrogenase; IPFT, intrapleural fibrinolytic therapy; DNAse, dornase alfa; CT, computed tomography.

early to prevent surgery. Some emerging data show that surgery should be performed early (55). However, this is not always feasible in the critically ill patient. MT be a viable alternative that can be performed at the bedside and allow for better drainage.

We recommend early empiric antibiotics and anaerobic coverage based on local antibiograms and de-escalating antibiotics once the organism has been identified or resistant organisms have been excluded. We also recommend the initial use of small-bore pleural drains (14 Fr) inserted under direct ultrasound guidance in combination with IPFT with 10 mg of tPA and 5 mg of DNAse every 12 hours for the treatment of CPE and pleural empyema (*Figure 3*).

Hemothorax

Introduction

The leading causes of hemothorax are blunt or penetrating thoracic trauma, and therefore the majority of cases are managed in the surgical ICU. The diagnosis of hemothorax is a surgical emergency, where there may be a need for immediate surgical exploration for the management of hemothorax (56). Rarely, a hemothorax can occur spontaneously (*Table 5*) (57,58).

Definition

Hemothorax is a collection of blood in the pleural space and is defined by a pleural fluid hematocrit >50% of the serum hematocrit. However, blood in pleural fluid gets diluted over 3–4 days by the process of osmosis, which may inadvertently lower the hematocrit below 50%. Therefore, hemothorax is still a possibility in the right clinical setting even when the pleural hematocrit may be <50% of the serum hematocrit (59).

Pathophysiology

Hemothorax can originate from intrathoracic vasculature, such as intercostal vessels, internal mammary vessels,

Table 5 Common causes of hemothorax

Etiology of hemothorax
Traumatic
Blunt thoracic trauma (e.g., motor vehicle accident)
Penetrating thoracic trauma (e.g., stabbing, gunshot)
Iatrogenic
Tube thoracostomy, thoracentesis, central venous catheterization
Spontaneous
Malignancy—lung cancer, renal cancer, vascular tumors, angiosarcomas, neurofibromatosis
Coagulopathy—IPFT complication, anticoagulation, hemophilia, thrombocytopenia
Miscellaneous—pulmonary embolism, thoracic endometriosis, hereditary hemorrhagic telangiectasia

IPFT, intrapleural fibrinolytic therapy.

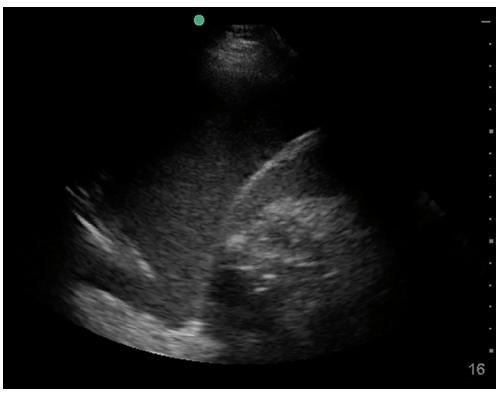

Figure 4 Hematocrit sign found on ultrasound in a patient with a hemothorax. The echogenicity of the fluid increases with depth.

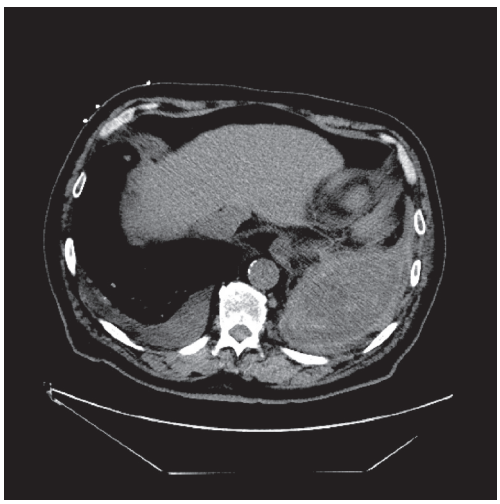

Figure 5 Thickened pleura from retained hemothorax.

aorta, and pulmonary vasculature. It can also come from extrathoracic origins, such as intrabdominal vessels. Once active bleeding stops, the fibrinolytic system attempts to lyse the clot. However, in cases where the fibrinolysis is incomplete, the clot can organize within the pleural space, resulting in the formation of pleural peel and lead to the development of trapped lung and/or fibrothorax (*Figure 3*).

Clinical presentation

Clinical presentation depends upon the rapidity of extravasation of the blood and underlying etiology. Massive hemothorax is defined as the accumulation of >1.5 L of the blood over 24 hours, which can have severe effects on the cardiopulmonary system such as hypotension, acute respiratory failure, and cardiopulmonary arrest.

Diagnosis

Early recognition and treatment of hemothorax can be lifesaving in patients with a hemothorax. Hemothorax should be considered in all patients with thoracic trauma. TUS is a quick, inexpensive, and sensitive screening tool for the detection of hemothorax during an initial trauma evaluation. Multiple studies have shown that TUS has a higher sensitivity than chest X-ray in detecting hemothorax in patients with blunt trauma (*Figure 4*) (60,61). Contrast-enhanced chest CT should be performed after the initial screening to identify the source of bleeding, which may also reveal an underlying etiology and the presence of injuries to vital organs (*Figure 5*) (62).

Management

Small hemothorax, in the absence of hemodynamical instability, can be managed conservatively with pain control and serial monitoring of the hemothorax size. Hemodynamically unstable patients should be aggressively resuscitated with blood transfusion and intravenous fluid (63). Tube thoracostomy is the mainstay of the management of moderate to large hemothorax. There is a theoretical concern of tube occlusion while using small-bore chest tubes. However, multiple studies have shown similar results between small-bore (14 French) and large bore (>28 French) chest tubes (64). Tube size is chosen based on personal preference. Regardless, tube occlusion and output should be closely monitored in patients with hemothorax. Surgical exploration via VATS or anterolateral thoracotomy may be required in patients who continue to have a large amount of active bleeding, defined as >1.5 L of blood in the first 24 hours, >200 mL per hour for 2–3 consecutive hours, or presence of vital organ injuries (65).

Survivors of hemothorax can develop a retained hemothorax (clotted blood occupying >1/3rd of hemithorax) if the hemothorax is not properly drained in a timely fashion. This may result in complications such as empyema, trapped lung, or even fibrothorax (65-67). Therefore, a retained hemothorax should be evacuated. Recent data suggest that IPFT may be equally effective in evacuating retained hemothorax (68). If IPFT fails, then surgical evacuation may be required (69).

Summary

Hemothorax generally occurs in the setting of trauma and is typically managed in the surgical ICU. Small hemothoraces can be managed conservatively, while larger ones will require drainage to prevent progression to fibrothorax. Although many experts still advocate for large-bore chest tubes, small-bore chest tubes are equally effective. IPFT therapy can be considered if there is inadequate drainage, but surgical evacuation is the definitive therapy for a retained hemothorax.

We recommend placement of small-bore chest tubes initially and upsizing to a large bore if there is inadequate drainage. Retained hemothorax can be managed by IPFT therapy in the critically ill patient, but if active bleeding is suspected, surgical evaluation is still the preferred method.

Pneumothorax

Pneumothorax can be classified into spontaneous or iatrogenic. Pneumothorax can be complicated by tension pneumothorax, hemopneumothorax, pyopneumothorax, and open pneumothorax. Pneumothorax is an independent predictor of mortality in patients on mechanical ventilation (70). Pneumothorax from barotrauma, concurrent pneumothorax with septic shock, and those who progress to tension pneumothorax were all significantly associated with increased mortality in the ICU (71). In this review, we will focus on the most common causes of pneumothorax in the ICU, including iatrogenic, and pneumothorax resulting from barotrauma/volutrauma (*Table 6*).

Definition

Pneumothorax is the accumulation of extra-alveolar air in the pleural space. There are six ways in which air can leak into the pleural space: (I) rupture or injury of the visceral pleura that allows for air to escape from the alveoli into the pleural space (e.g., barotrauma or volume trauma); (II) entry of air from the atmosphere due to chest trauma or iatrogenic needle injury; (III) rupture of adjacent hollow viscous (e.g., Boerhaave's syndrome); (IV) transdiaphragmatic spread of air from the abdomen, (V) excess production from gas-forming organisms in the pleural space; and (VI) secondary rupture of the mediastinal pleura from a pre-existing pneumomediastinum which is believed is the most common pathogenic mechanism in secondary spontaneous pneumothorax (72).

Clinical presentation

Pneumothorax can be challenging to recognize in the critically ill patient. Acute onset of dyspnea or chest pain, tachycardia, hypotension, pulsus paradoxus, contralateral tracheal deviation, and sudden increase in peak and plateau pressure in a mechanical ventilated patient can point at a diagnosis. Physical exams and other clinical signs are unreliable and nonspecific. Confirmation by imaging is still necessary to make the diagnosis (73).

Diagnosis

CXR is still the most commonly used tool to diagnose a pneumothorax. An anteroposterior portable CXR in a

Table 6 Etiologies of pneumothoraces in patients in the intensive care unit

Etiologies of pneumothorax in critically ill patients
Traumatic
Chest trauma—rib fractures, blunt chest trauma, penetrating chest trauma
Esophageal rupture (e.g., Boerhaave's syndrome)
Tracheobronchial injuries
Barotrauma—inhalation drug use, decompression injury
Iatrogenic
Mechanical ventilation (e.g., barotrauma in ARDS)
Thoracentesis
Central line placement
Endotracheal intubation
Nasogastric tube placement
Tracheostomy
Bronchoscopy with BAL or biopsy
Post cardiopulmonary resuscitation
Post-surgical
Spontaneous
Airway disease—COPD, Asthma, fibrosis
Parenchymal disease—pulmonary langerhans histiocytosis, Interstitial lung disease
Infections—pneumocystis jirovecii, necrotizing pneumonia (e.g., bronchopleural fistula)

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; BAL, bronchoalveolar lavage.

supine patient is unreliable for diagnosing pneumothorax in the ICU (9,74). Increasing evidence suggests that thoracic US, in a set of experienced hands, can be accurate in diagnosing a pneumothorax. The absence of pleural sliding next to the presence of pleural sliding, known as lung point sign, is 100% specific for pneumothorax (75). The diagnostic accuracy of portable CXR was only 46% compared to 87% with US (74).

Chest CT remains the gold standard for diagnosing and evaluating the size of a pneumothorax. However, this requires patient transport and delays the diagnosis, which may be unacceptable in a hemodynamically unstable patient.

Management

Tension pneumothorax is a medical emergency, and delay in therapy can lead to respiratory and hemodynamic decline leading to death. This is especially true for patients on mechanical ventilation (76). Pneumothorax should be suspected when there is sudden worsening in oxygenation, increased tachycardia, tachypnea, or worsening in lung compliance (77). When therapy cannot be delayed for confirmation, immediate needle decompression should be performed with a large-bore (14- to 16-gauge) anigocatheter attached to a syringe filled with fluid between the 4th and 5th intercostal space at the mid- or anterior-axillary line (78,79). Chest tube can be initially considered, if the provider is experienced and if materials are immediately available. If needle decompression is used, a chest tube should then be inserted once the patient has been stabilized to prevent further decompensation.

A small-bore chest tube is comparable to a large-bore chest tube when treating pneumothorax in mechanically ventilated patients (71,80). If a small-bore catheter fails to drain the air adequately, then a large-bore chest tube should be placed. Insufficient evacuation of air from the pleural space may be indicated by worsening subcutaneous emphysema. This finding can be identified by regular

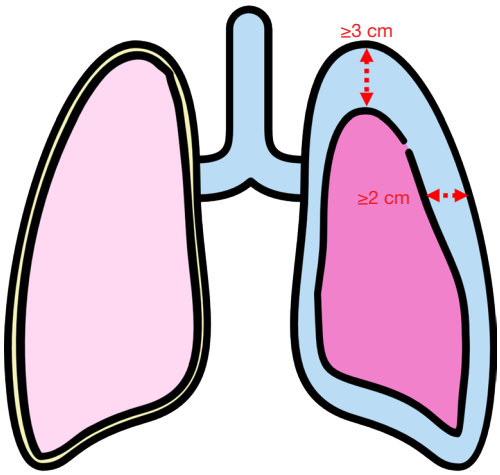

Figure 6 Pneumothorax is classified as large on a frontal chest X-ray if the distance from the margin of the lung to the chest wall is 2 cm from the chest wall at the level of hilum or 3 cm from the apex of the lung. On CT scan a large pneumothorax occupies >20% of the ipsilateral hemithorax.

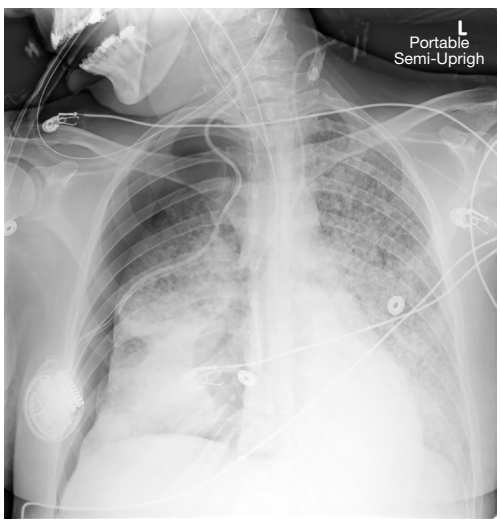

Figure 7 Large right sided pneumothorax on frontal portal chest X-ray in a patient on mechanical ventilation occurring after the patient had a chest wall biopsy.

palpation around the chest tube insertion site to identify expanding crepitus. Blunt dissection technique or CT guided placement of chest tube should be performed in the presence of large bullae.

The application of negative intrathoracic suction via the chest tube has been advocated for the therapy for pneumothorax in order to reduce the amount of air and allow for quick lung re-expansion, by reducing the pleural pressure back to its normal resting state. Suction with a high-volume, low-pressure system is generally desired. Such a system provides for the removal of large air leaks but not cause an excessive drop in pleural pressure. Optimal suction should be conducted with pressures of –10 to –20 cmH_2O (81,82).

In the non-mechanically ventilated patient, management should depend on how the patient is affected clinically and the pneumothorax size (*Figure 6*) (81,83). In a patient with a sufficient physiological reserve, it may be reasonable to observe a small iatrogenic pneumothorax. In a study of trauma patients with occult pneumothoraces, there was no difference in outcomes with or without chest tube insertion (84,85).

However, the majority of patients on mechanical ventilation with a small pneumothorax will progress to tension physiology and intervention is recommended (*Figure 7*) (86,87). If the pneumothorax is not large enough for chest tube placement, then careful monitored with serial X-rays and pleural US should be conducted.

In most cases when the air leak resolves and the lung re-expands, the chest tube can be removed. However, when an air leak persists >5 days, which defines a persistent air leak, then more definitive therapy may need to be pursued (88). If patients are on mechanical ventilation, then the liberation from the ventilator should be performed before definitive treatment to close the air leak. Patients with persistent air leaks should have their mean airway pressure and suction pressure minimized to promote air leak closure. If the patient displays possible unexpandable lung physiology, manometry may help in differentiating in the diagnosis of an unstable air leak, which may require more definitive therapies (89,90). Many critically ill patients may not remain a good candidate for a surgical procedure. Therefore, bronchoscopic techniques, especially with more recent refinements, should be considered. Discussion of such procedures is beyond the scope of this review. We recommend the management algorithm shown in *Figure 8*.

Summary

The diagnosis of pneumothorax can be challenging on portable CXR. Chest CT is the gold standard for the diagnosis but may not be feasible in the critically ill patient. US is a quick and accurate way of ruling in pneumothorax when lung-point sign is identified. The

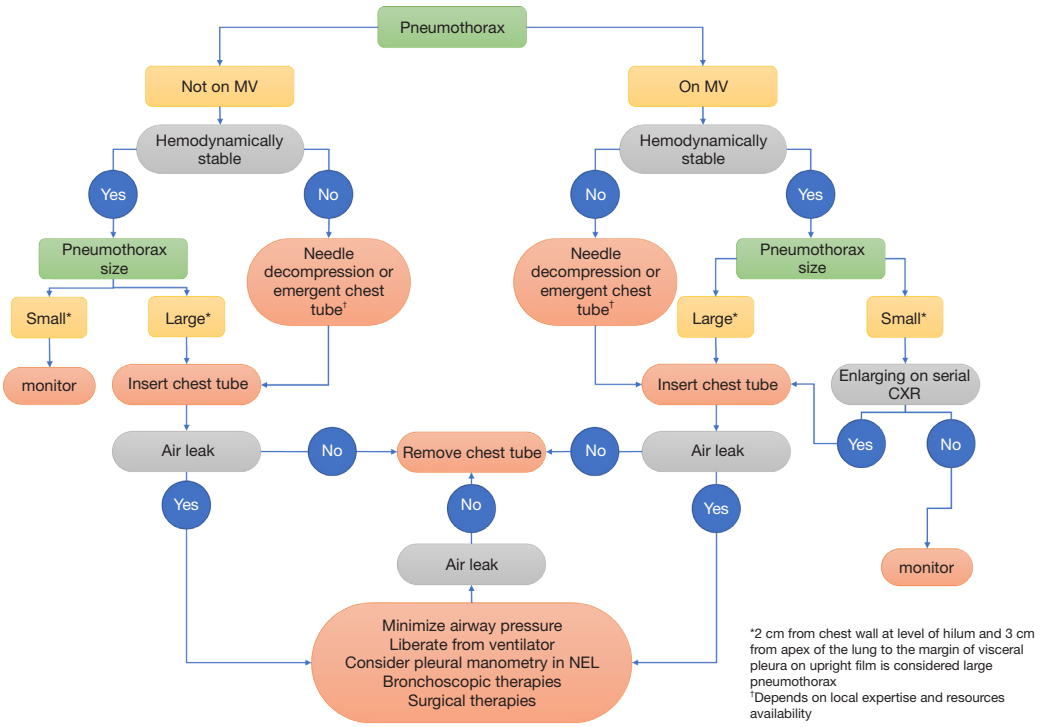

Figure 8 Algorithm for management of pneumothorax in the ICU. MV, mechanical ventilation; NEL, non-expandable lung.

presence of lung sliding does not always mean the absence of a pneumothorax. The cornerstone of therapy is pleural drainage and is especially important when patients are on mechanical ventilation. Conservative management includes optimizing ventilator pressures and applying suction to actively evacuate the air. Once liberated from the ventilator, more definitive therapies can be performed.

We recommend the placement of small-bore chest tubes (<15 Fr) under Seldinger technique for the initial management of a pneumothorax. If a small-bore chest tube is inadequate, then placement of a large-bore chest tube with blunt dissection should be performed. If there is a concern for bullous disease, then CT-guided placement is recommended (*Figure 8*).

Pleural fluid of extravascular origin (PEEVO)

PEEVO is a rare type of pleural effusion that does not originate from the pleural vasculature and results from the migration of fluid from an extra-pleural space such as the abdomen, the genitourinary system, the biliary system, or the central nervous system (91,92). PEEVO is a rare cause of pleural effusion in critically ill patients. However, the diagnosis can be very challenging. Often patients with PEEVO undergo multiple pleural procedures before the diagnosis is made, and therefore, a high index of suspicion is needed in the appropriate clinical context. *Table 7* summarizes various causes of PEEVO. Specific details of each cause of PEEVO is beyond the scope of this review (2).

Conclusions

Pleural disorders can be hard to diagnose in patients in the ICU. CXR may not always be helpful due to the underlying lung pathology. US has revealed itself to be a useful tool for the bedside clinician. Management of disorders such as CPE, hemothorax, and pneumothorax, can require additional expertise. Drainage remains the hallmark therapy for many pleural disorders. Although there is abundant data that shows that small-bore chest tube is comparable to large-bore chest tube in most pleural space disorders, there has yet to be any randomized controlled trial. Intrapleural therapy for CPE/empyema is widely accepted to reduce surgical referral and may help with the clearance of pleural sepsis. As we continually advance the understanding of the physiological processes and improve in diagnostics, there will be further refinement of therapies.

Table 7 A list of pleural effusion of extravascular origin (PEEVO) that can be encountered in the ICU

PEEVO type	Fluid type	When to suspect	Pleural fluid analysis	Diagnostic test
Transudative				
Urinothorax	Urine	Ipsilateral GU tract lesion	Serous, transudate with very low protein (<1 mg/dL), pH <7.40	PF/S creatinine >1
VP or VPL shunt DPF	CSF	VP or VPL shunt Spinal cord tumor, neurosurgical or thoracic surgery	"clear water" appearance with very low protein (<1 mg/dL)	β_2-transferrin present
EVM of CVC	Intravenous fluid	Development of ipsilateral effusion after newly placed CVC that is malfunctioning	Serosanguinous (if mixed with blood) with very low protein, content of infusion fluid	High glucose if dextrose containing fluid
PLAPD	Peritoneal dialysate	Peritoneal dialysis	Clear fluid, transudate with very low protein (<1 mg/dL)	Glucose 200–2,000 mg/dL
Glycinothorax	Irrigation fluid rich in glycine	Trans-urethral bladder surgery	Clear fluid, transudate	PF/S glycine 300:1 or higher
Hepatic hydrothorax	Ascites	Effusion in a patient with portal hypertension	Clear transudate similar to ascites (unless infected)	Clinical diagnosis; intraperitoneal injection of 99mTc-sulpur colloid or 99mTc-human albumin
Exudative				
Esophageal or gastric perforation	Infected or esophageal/ gastric content	Esophageal injury, malignancy, Boerhaave syndrome, often left sided effusion	Purulent, foul odor, exudate with: high PMN, LDH >1,000 IU/L, low pH 5-7	PF/S amylase >1 IU/L of salivary origin, presence of food particles
Bilothorax	Bile	Injury to the biliary tree, biliary obstruction or parasitic infection of liver, right sided	Green and turbid, exudate with sign of infection, high LDH, pH <7.2, low glucose	PF/S bilirubin >1 (organisms may be present)
Pancreatico-pleural fistula	Pancreatic fluid	Chronic pancreatitis, pseudocyst, often right-sided effusion	Turbid yellow, exudate	Amylase >100,000 IU/L of pancreatic origin
Enteral feeding tube migration	Enteral formula	Misplaced feeding tube with left side effusion	Milky fluid with high TG	TG >110 mg/dL, PF/S glucose >1
Chylothorax	Chyle (lymphatic fluid)	Lymphatic pathology (e.g., tumors, trauma, LAM)	Milky fluid with high TG	TG >110 mg/dL or detection of chylomicrons
Cholesterol effusion	Cholesterol	Effusion in patient with TB or RA	Milky fluid	PF cholesterol >200 mg/dL, a cholesterol to TG ratio >1, absence of chylomicrons

GU, genitourinary; PF/S, pleural fluid/serum fluid; VP or VPL, ventriculoperitoneal or ventriculopleural; DPF, duropleural fistula; EVM of CVC, extravascular migration of central venous catheter; PLAPD, pleural effusion associated with peritoneal dialysis; PMN, polymorphonuclear leukocytes; LDH, lactic acid dehydrogenase; IU, international units; TG, triglyceride; LAM, lymphangioleiomyomatosis; TB, tuberculosis; RA, rheumatoid arthritis. Reproduced with permission from: Chopra A, Huggins JT. Pleural effusion of extra-vascular origin (PEEVO). In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on 6/29/2020.) Copyright© 2020 UpToDate, Inc. For more information visit www.uptodate.com.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease* for the series "Interventional Pulmonology in the Intensive Care Unit Environment". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: https://dx.doi.org/10.21037/jtd-2021-31). The series "Interventional Pulmonology in the Intensive Care Unit Environment" was commissioned by the editorial office without any funding sponsorship. JK served as the unpaid Guest Editor of the series. JK reports personal fees from Level Ex, personal fees from Medtronic, other from Pinnacle Biologics, personal fees from Biodesix; personal fees from American Medical Forum, and outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Hu K, Chopra A, Kurman J, Huggins JT. Management of complex pleural disease in the critically ill patient. J Thorac Dis 2021;13(8):5205-5222. doi: 10.21037/jtd-2021-31