Official Journal of the Asian Pacific Society of Respirology
Respirology

REVIEW

Getting the most from pleural fluid analysis

STEVEN A. SAHN

Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

ABSTRACT

Virtually, every pulmonary disease and most non-pulmonary diseases may be associated with a pleural effusion. The presence of a pleural effusion allows the clinician to 'diagnose' or narrow the differential diagnosis and aetiology of the fluid collection. However, pleural fluid analysis (PFA) in isolation rarely provides a definitive diagnosis. This review discusses the rationale for evaluating patients with a pleural effusion. If the clinician obtains a detailed history, performs a comprehensive physical examination, reviews pertinent blood tests, and evaluates the chest imaging findings prior to thoracentesis, there should be a high likelihood of establishing a firm clinical diagnosis based on the appropriate PFA. This manuscript reviews the clinical presentation, chest imaging findings, duration and natural course of specific pleural effusions to help narrow the range of pre-thoracentesis diagnoses. A diagnosis of transudative effusion confirms an imbalance in hydrostatic and oncotic pressures, normal pleura and a limited differential diagnosis, which is typically apparent from the clinical presentation. Exudates are the result of infections, malignancies, inflammation, impaired lymphatic drainage or the effects of drugs, and pose a greater diagnostic challenge. The differential diagnosis for a pleural exudate can be narrowed if LDH levels exceed 1000 IU/L, the proportion of lymphocytes is ≥80%, pleural fluid pH is <7.30 or there is pleural eosinophilia of >10%.

Key words: exudates, pleural fluid, pleural fluid analysis, transudates.

Once the lung is fully developed, the visceral and parietal pleura are separated by a potential space containing glycoprotein-rich fluid to a depth of 10–20 μm. It has been estimated that this fluid amounts to 0.1–0.2 mL/kg in total in adults. Normal pleural fluid has a protein concentration of approximately 15 g/L. The fluid itself is paucicellular with small numbers of macrophages, mesothelial cells and lymphocytes.[1] The parietal pleura derives its blood supply from the intercostal arteries.[2] It is believed that the visceral pleura derives most of its blood supply from the bronchial arterial system. The lymphatics of the visceral and parietal pleura are important for homeostasis of pleural fluid volume in the normal state. A fundamental component of lymphatic abnormality is the existence of naturally occurring pores (stomata) in areas of the peripheral parietal pleura and lower mediastinal pleura. It is through these pores that particulate matter and cells move directly into the lymphatic channels. Most of the fluid that accumulates in the pleural spaces derives from the lungs through the visceral pleura and is absorbed primarily through the parietal pleura.

There are five pathophysiological mechanisms responsible for the accumulation of pleural fluid: (i) increased transpleural pressure (e.g. congestive heart failure (CHF)); (ii) increased capillary permeability (e.g. parapneumonic effusion); (iii) impaired lymphatic drainage (e.g. malignancy); (iv) transdiaphragmatic movement of fluid from the peritoneal space (e.g. hepatic hydrothorax); and (v) pleural effusion of extravascular origin (PEEVO) (e.g. chylothorax and peritoneal dialysis). PEEVO may be transudates or exudates (Table 1).[3]

PLEURAL EFFUSIONS: A MANIFESTATION OF PULMONIC AND EXTRA-PULMONIC DISEASE

Most lung and systemic diseases may be associated with a pleural effusion based on the mechanisms discussed previously. Perhaps, one of the only diseases that is not commonly associated with a pleural effusion is moderate to severe IPF, as sub-visceral pleural fibrosis tends to prevent movement of fluid from the lung interstitium into the pleural space. The inability to clear fluid resulting from pulmonary oedema and entering the pleural space in patients with IPF may explain the frequent occurrence of hypoxaemia-induced death in these patients.

Correspondence: Steven A. Sahn, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, 96 Jonathan Lucas Street, CSB Room 812, Charleston, SC 29425, USA. Email: sahnsa@musc.edu

Received 11 August 2011; invited to revise 28 August 2011, 10 September 2011; revised 30 August 2011, 12 September 2011; accepted 23 September 2011 (Associate Editor: José Porcel).

Table 1 Pleural effusion of extravascular origin (Data taken from Sahn[3])

Transudates	Exudates
• Duropleural fistula	• Biliopleural fistula
• EVM of CVC (saline or glucose)	• Chylothorax
• Glycinothorax	• Enteral tube feeding
• Peritoneal dialysis	• Oesophageal rupture
• Urinothorax	• EVM of CVC (TPN)
• Ventriculoperitoneal shunt migration	• Gastropleural fistula
• Ventriculopleural shunt	• Pancreaticopleural fistula

CVC, central venous catheter; EVM, extravascular migration; TPN, total parenteral nutrition.

Table 2 'Definitive' diagnosis of transudates by pleural fluid analysis (Data taken from Sahn[3])

Peritoneal dialysis	Ventriculoperitoneal shunt migration and ventriculopleural shunt
• Total protein < 5 g/L	• Presence of B2 transferrin
• Glucose > 2 000–20 000 mg/L	Spontaneous bacterial pleuritis in hepatic hydrothorax
EVM of CVC (glucose)	• ANC > 500/μL
• Total protein < 10 g/L	• ANC > 250/μL with positive Gram stain
• PF/S glucose substantially > 1.0 up to 30 000 mg/L	
Urinothorax	
• PF/S creatinine > 1.0	
Duropleural fistula	
• Presence of B2 transferrin	

ANC, absolute neutrophil count; CVC, central venous catheter; EVM, extravascular migration; PF, pleural fluid; S, serum.

Table 3 'Definitive' diagnosis of exudates by pleural fluid analysis (Data taken from Sahn[4])

Oesophageal rupture	Acute pancreatitis
• pH 5.00–7.00	• Amylase 200–2 000 IU/L
• Elevated salivary amylase	Pancreaticopleural fistula
Chylothorax	• Amylase > 100 000 IU/L
• Triglycerides > 1100 mg/L	• Neutrophils predominant
• Chylomicrons present	Malignancy
Lupus pleuritis	• Positive cytology
• LE cells present	Empyema
Haemothorax	• Pus
• PF/blood HCT ≥ 0.5	Biliopleural fistula
	• PF/S bilirubin > 1.0
	Cholesterol effusion
	• Cholesterol > 2500 mg/L
	• Satin-like sheen

HCT, haematocrit; LE, lupus erythematosus; PF, pleural fluid; S, serum.

PLEURAL FLUID ANALYSIS (PFA) IN ISOLATION WILL MOST LIKELY BE NON-DIAGNOSTIC

Most lung and systemic diseases cannot be diagnosed with a high degree of clinical confidence based on PFA alone, in the absence of culture and cytology studies. These diagnoses are listed in Tables 2 and 3.[4] The clinician must start with a detailed history, a thorough physical examination, interpretation of blood tests and careful review of chest imaging findings, in addition to ultrasonography of the chest. All this information should be integrated prior to thoracentesis to increase the likelihood of reaching a firm clinical diagnosis.

CLINICAL PRESENTATION

The clinician should always investigate the duration of the effusion,[5] previous pneumonia or pleurisy, and coronary artery bypass graft (CABG) surgery,[6] especially that associated with harvesting of the internal mammary arteries; the latter may result in an unexpandable lung as the cause of an unexplained transudate months or years later. A history of, and radiation treatment for, malignancy may also cause an unexpandable lung. Remote asbestos exposure may cause a benign asbestos pleural effusion (BAPE).[7] The clinician should always inquire about place of residence and travel history, as fungi, particularly histoplasma (15% incidence)[8] and coccidioides (15% incidence),[9] may cause pleural effusions. Drugs should always be considered as a potential cause of exudates of unknown aetiology;[10] the website http://www.Pneumotox.com may be helpful in this regard.

Lastly, the time of the re-accumulation of pleural fluid following therapeutic thoracentesis should be noted. When there is rapid re-accumulation (within 24–72 h) of most of the pleural fluid following therapeutic thoracentesis, the clinician should consider transudative causes, such as trapped lung, peritoneal dialysis, hepatic hydrothorax and extravascular migration of a central venous catheter, with saline or glucose infusion. Exudates that recur rapidly following thoracentesis include those due to aggressive vascular tumours, such as angiosarcoma and chylothorax (Table 4). A person eating a normal diet produces up to 2400 mL of chyle daily. Lung entrapment occurs as a result of malignancy in about 50% of patients,[11] in addition to other comorbidities, such as parapneumonic effusions. Malignant ascites and peritoneal fluid from Meigs syndrome may cause pleural fluid to re-accumulate rapidly due to the pressure gradient across the diaphragm. Lastly, blood can accumulate rapidly following an iatrogenic haemothorax.

SILENT AND SYMPTOMATIC PLEURAL EFFUSIONS

Both transudates and exudates may be detected on CXR and not be associated with symptoms. Causes

Table 4 Rapid (24–72 h) reaccumulation of pleural fluid following thoracentesis

Transudates	Exudates
• EVM of CVC with glucose/saline	• Angiosarcoma
• Hepatic hydrothorax	• Chylothorax
• Peritoneal dialysis	• Iatrogenic haemothorax
• Trapped lung	• Lung entrapment
• Urinothorax	• Malignant ascites
	• Meigs syndrome

CVC, central venous catheter; EVM, extravascular migration.

of 'silent' transudative pleural effusions include atelectasis, which is commonly seen in patients in intensive care units,[12] and hypoalbuminaemia.[13] Less than 2% of peritoneal dialysis patients develop a small, right-sided pleural effusion without symptoms.[14] However, multiparous women may develop rapid onset, massive right pleural effusions within a few days of starting peritoneal dialysis, and these always cause dyspnoea, as pregnancy can exacerbate diaphragmatic defects.[15,16] Dyspnoea may occur many years after CABG surgery[6] or pneumonia due to a trapped lung. Silent exudative effusions may also occur with rheumatoid pleural effusions,[17] tuberculous empyema,[18] BAPE,[7] and yellow nail syndrome.[19]

Transudates that virtually always present with symptoms include those due to CHF, constrictive pericarditis, extravascular migration of a central venous catheter and hepatic hydrothorax. Exudates that typically present with chest pain include those due to bacterial pneumonia, lupus pleuritis, mesothelioma, post-cardiac injury syndrome (PCIS), pulmonary embolism and viral pleurisy.[20]

CHEST IMAGING

A pleural effusion may be the only abnormality detected on chest imaging; this is observed with both transudates and exudates. Transudates with a solitary pleural effusion typically involve diseases of the liver and kidneys; examples include those due to hepatic hydrothorax,[21] hepatitis, nephrotic syndrome,[22] peritoneal dialysis,[16] and urinothorax.[23] Exudates with solitary pleural effusions include those due to acute pancreatitis,[24] pancreaticopleural fistula,[25] chylous ascites,[26] Meigs syndrome[27] and subphrenic abscesses.[28]

When the CXR reveals a massive pleural effusion that occupies the entire hemithorax, malignancy is the most common cause;[29] approximately 70% of massive effusions are due to malignancies. If there is contralateral mediastinal shift, the malignancy is usually a non-lung primary. When there is absence of or ipsilateral mediastinal shift, lung cancer involving the ipsilateral mainstem bronchus is usually the cause; this radiographic feature is also observed with a fixed mediastinum or malignant mesothelioma.

When the CXR or CT shows bilateral pleural effusions with a normal cardiac size, the most common diagnosis appears to be malignancy;[30] other exudates that may present with this radiological feature include lupus pleuritis and oesophageal rupture. Approximately 15% of patients with a hepatic hydrothorax will develop bilateral pleural effusions, and those with nephrotic syndrome may have small, bilateral pleural effusions. Patients with CHF and bilateral effusions with a normal heart size typically present in the setting of acute myocardial infarction[30] and constrictive pericarditis.

Pleural effusions associated with pulmonary nodules most commonly include those due to metastatic carcinomas and Wegener's granulomatosis,[31] rheumatoid arthritis,[32] septic emboli[33] and tularemia.[34]

PLEURAL EFFUSIONS WITH INTERSTITIAL INFILTRATES OR NODULES

The most common pleural effusion with interstitial infiltrates is that due to CHF. Twenty percent of patients with viral and mycoplasma pneumonia have small pleural effusions.[35] The prevalence of chylothorax in patients with lymphangioleiomyomatosis is about 20% during their lifetime.[36] BAPE is one of the earliest manifestations of asbestos exposure and is associated with asbestosis in 7% of cases.[7] Approximately 5% of patients with rheumatoid arthritis develop pleural effusions; these patients are usually men with active rheumatoid disease.[17] Less than 5% of patients with *Pneumocystis jiroveci* pneumonia may develop a pleural effusion,[37] and less than 2% of patients with sarcoidosis have exudative pleural effusions.[38] Lymphangitic carcinomatosis, which occurs in patients with metastatic adenocarcinoma, presents with the classical triad of unilateral pleural effusion, unilateral mediastinal lymphadenopathy, and Kerley B lines.[39]

RESOLUTION OF PLEURAL EFFUSIONS: SPONTANEOUS OR FOLLOWING TREATMENT

It is helpful to determine the chronicity of symptoms in individuals presenting with a pleural effusion.[5] In general, effusions that resolve within 2 weeks of the initial presentation, with or without treatment, include those due to acute pancreatitis, atelectasis and CHF with treatment; those occurring post-lung, heart and liver transplantation; and those due to pulmonary embolism without infarction,[40] traumatic chylothorax[41] and urinothorax.[23]

Patients whose effusions resolve within 2 months include those with acute pancreatitis, lupus pleuritis treated with corticosteroids,[42] parapneumonic effusions, PCIS with or without corticosteroid therapy;[6] those presenting post-lung, heart and liver transplantation;[43] those with sarcoidosis treated with

corticosteroids;[44] those with treated or untreated tuberculous pleural effusions;[45] and those with uraemic pleural effusions who continue with dialysis.[46] It is important to note that a tuberculous pleural effusion will resolve after 4–16 weeks, with or without treatment; however, if the patient is not treated with anti-tuberculous chemotherapy, there is a chance that up to 65% of individuals may develop active pulmonary or extra-pulmonary tuberculosis within the next 5 years.[47]

Untreated pleural effusions that resolve within 2–6 months include BAPE, effusions due to pancreaticopleural fistula, effusions occurring post-CABG surgery, rheumatoid effusions and tuberculous pleural effusions.[5] Effusions that typically persist for 6 months are limited to BAPE, effusions occurring post-CABG surgery and rheumatoid pleural effusions.[5]

BENIGN, PERSISTENT PLEURAL EFFUSIONS

Benign, persistent pleural effusions include the unexpandable lung, both trapped lung and lung entrapment, as seen with cholesterol effusions,[47] lymphatic abnormalities[19] and the effects of drugs.[5,10] The most common lymphatic abnormalities resulting in pleural effusions include chylothorax in the setting of lymphangioleiomyomatosis, Noonan's syndrome, yellow nail syndrome and any form of lymphangiectasis. There are three causes of an unexpandable lung: (i) chronic atelectasis; (ii) an endobronchial lesion, most commonly lung cancer; and (iii) visceral pleural restriction.[47] A trapped lung occurs when there is visceral pleural thickening due to a remote, inflammatory or infectious process, most commonly pneumonia or haemothorax.[47] Lung entrapment defines a process that produces visceral pleural restriction, with a concomitant active pleural process that contributes to the development of the effusion. Causes of lung entrapment include malignancies, rheumatoid pleurisy,[32] chronic tuberculous empyema[18] and cholesterol pleural effusions;[41] the most common cause of a cholesterol-rich effusion is tuberculosis, and less commonly, rheumatoid arthritis.

DETERMINING THE CAUSE OF PLEURAL EFFUSIONS

The colour of the effusion may be helpful in narrowing the differential diagnosis.[48] For example, a pale yellow fluid usually indicates a transudate or, less commonly, a paucicellular exudate. If the effusion is haemorrhagic, in the absence of prior trauma or blood vessel disruption associated with needle insertion, the differential diagnosis is limited to malignancy, BAPE, PCIS and pulmonary infarction.[48] A 'milky' effusion is most commonly due to chylothorax but may also indicate a chronic cholesterol pleural effusion.[49] A fluid with a yellowish-green tint is suggestive of rheumatoid effusion, and green fluid suggests a biliopleural fistula.[50]

The viscosity of the pleural fluid may also be diagnostically helpful. If the fluid resembles water, it is probably the result of a duropleural fistula.[51] Pus, which contains intravascular clotting proteins, degenerate cells and products of fibrosis, produces a yellowish-white, opaque, viscous effusion that is diagnostic for empyema. Viscous fluid that is not due to empyema may be the result of high levels of hyaluronic acid, and suggests malignant mesothelioma. Pleural fluid cytology that identifies debris with multinucleated, tadpole-shaped giant cells is virtually diagnostic of a rheumatoid pleural effusion.[52] Pleural fluid with a satin-like sheen suggests a cholesterol pleural effusion.[49] When pleural fluid has a putrid odour, anaerobic empyema is the most likely cause; however, only 50% of anaerobic empyemas have a putrid odour.

TRANSUDATES AND EXUDATES

Following observation of the fluid, the next step is to determine whether the fluid is a transudate or an exudate. Transudates are due to imbalances in hydrostatic and oncotic pressures, although the pleura are normal. The differential diagnosis is limited, and the cause should be apparent from the clinical presentation.[3,48,53,54] Transudative effusions are clear yellow with a total nucleated cell count of <500/μL. The pleural fluid/serum protein ratio is ≤0.50, and the pleural fluid LDH/upper limit of normal serum LDH is ≤0.67. Pleural fluid glucose is equivalent to the serum glucose level, and pleural fluid pH typically ranges from 7.45 to 7.55. Pleural fluid cholesterol is ≤520 mg/L, and the albumin gradient (serum albumin minus pleural fluid albumin) is ≥12.0 g/L.[44,55] The causes of transudative effusions are shown in Table 5. CHF and hepatic hydrothorax cause approximately 70% of all transudates. When the clinician confirms a transudate and the pleural fluid protein concentration is <10 g/L, the diagnoses that should be considered are PEEVO effusions, and include (i) a duropleural fistula; (ii) extravascular migration of a central venous catheter, with saline or 5% dextrose (D5W) infusion; (iii) peritoneal dialysis; (iv) urinothorax; (v) a ventriculopleural shunt; and (vi) migration of a ventriculoperitoneal shunt.[3]

Table 5 Causes of transudative pleural effusions (Data taken from Sahn[3])

• Congestive heart failure	• Constrictive pericarditis
• Hepatic hydrothorax	• EVM of CVC with saline/glucose
• Hypoalbuminaemia	• Urinothorax
• Trapped lung	• Duropleural fistula
• Nephrotic syndrome	• Glycinothorax
• Atelectasis	• Ventriculopleural shunt
• Peritoneal dialysis	• Ventriculoperitoneal shunt migration

CVC, central venous catheter; EVM, extravascular migration.

Exudates are caused by infections, malignancies, inflammation, impaired lymphatic drainage or drugs.[48,54,56] Exudates have an appearance that varies from a turbid effusion to milky in character, haemorrhagic or with a greenish tint. Total nucleated cell counts range from 500 to >100 000/μL. If the effusion is acute, neutrophils will predominate. With chronic effusions, lymphocytes and macrophages predominate. The pleural fluid/serum total protein ratio for exudates is >0.50, and the pleural fluid LDH/upper limit of normal serum LDH is >0.67.[56] The pleural fluid glucose concentration is equal to that of serum. The cholesterol concentration of an exudate is >550 mg/L,[54] and the albumin gradient is <12 g/L.[55] A pleural fluid protein concentration of 70–80 g/L suggests a paraproteinaemia, such as multiple myeloma[57] or Waldenstrom macroglobulinaemia.[58] Exudates that consistently have a total pleural fluid protein concentration of >40 g/L include cholesterol effusions[53] and tuberculous pleurisy.[53] When the pleural fluid exudate has an LDH level of >1000 IU/L, the differential diagnosis can be narrowed to empyema, a complicated parapneumonic effusion, a cholesterol pleural effusion, paragonimiasis, rheumatoid pleurisy or body cavity lymphoma, in which the LDH level may exceed 10 000 IU/L[59] (Table 6). Of the previous diagnoses, only chylothorax, sarcoidosis and yellow nail syndrome are protein-discordant exudates.[19,59]

If the cause of an exudate is unclear, a review of all medications is warranted. Five drugs that have each caused over 100 pleural effusions are listed in Table 7. In most cases, the total nucleated cell count does not provide a specific diagnosis. However, in general, most transudates have a total of <300 nucleated cells/μL and most exudates have >500 cells/μL. When the effusion contains >10 000 nucleated cells/μL, the differential diagnosis can be narrowed to uncomplicated parapneumonic effusion, acute pancreatitis, pulmonary infarction, lupus pleuritis, acute rheumatoid pleurisy and PCIS.[54,56,59] An effusion with a total of >50 000 nucleated cells/μL suggests a differential diagnosis of complicated parapneumonic effusion and pancreaticopleural fistula.[54,56,59] When there are >100 000 cells/μL, the diagnosis is empyema, which could be due to either bacteria or *Mycobacterium tuberculosis*.

In these difficult financial times, the use of a urinometer and protometer at the bedside may eliminate the need for other laboratory tests when protein levels and specific gravity are very low.

Table 6 Lymphocyte-predominant (≥80%) exudative effusions (Data taken from Sahn[4])

- Acute lung rejection
- Chronic rheumatoid pleurisy
- Chylothorax
- Lymphoma
- Post-coronary artery bypass graft surgery (2–12 months)
- Sarcoidosis
- Tuberculous effusion
- Uraemic pleural effusion
- Yellow nail syndrome

Table 7 Drug-induced pleural effusions (>100 cases reported) (Data taken from http://www.Pneumotox.com)

- Amiodarone
- Beta-blocker
- Methotrexate
- Nitrofurantoin
- Phenytoin

PLEURAL FLUID EOSINOPHILIA

Pleural fluid eosinophilia (PFE) is defined as >10% of the cells being eosinophils.[60–64] The two most common causes of PFE are pneumothorax and haemothorax.[61–64] In pneumothorax, eosinophils traffic to the area within hours of air entering the pleural space.[61] In haemothorax, eosinophilia will not develop for 10–14 days after blood has entered the pleural space.[61] Approximately 30% of patients with BAPE present with PFE. Other causes of PFE include pulmonary infarction resulting in pleural haemorrhage, parasitic disease particularly paragonimiasis, fungal disease due to either coccidioides or histoplasma, and drugs such as nitrofurantoin and valproic acid.[63] Lastly, about 8% of patients with lymphoma or carcinoma may present with PFE.[61,63,64] Nitrofurantoin and propylthiouracil have been reported to cause 20 to >100 cases of drug-associated PFE.[8]

PLEURAL FLUID pH

Most exudates have a pH ranging from 7.44 to 7.30.[65,66] However, small numbers of exudates have a pH < 7.30 (pleural fluid acidosis).[65,66] The eight types of exudative effusions associated with a pH < 7.30 are shown in Table 8.[65,66] In virtually all patients with a complicated parapneumonic effusion or empyema,

Table 8 Exudates with pleural fluid acidosis (pH < 7.30) (Data taken from Good[65])

	pH range	~Incidence (%)
• Complicated parapneumonic effusion/empyema ($n \geq 200$)	5.50–7.29	100
• Oesophageal rupture ($n = 15$)	5.50–7.00	100
• Chronic rheumatoid pleurisy ($n = 30$)	6.85–7.05	100
• Cholesterol effusion ($n = 5$)	<7.20	100
• Malignancy ($n = 175$)	6.95–7.29	20
• Tuberculous pleurisy ($n = 30$)	7.00–7.29	15
• Acute lupus pleuritis ($n = 25$)	7.00–7.29	15
• Paragonimiasis (n unknown)	<7.10	Unknown

oesophageal rupture (an anaerobic empyema), chronic rheumatoid pleural effusion or a cholesterol pleural effusion, the pleural fluid will have a pH < 7.30, and the pH may be as low as ≤6.00 in patients with oesophageal ruptures.[65] Patients with a malignant pleural effusion, tuberculous pleural effusion[67] or acute lupus pleuritis have a lower incidence of pleural fluid acidosis, and pH values are not lower than 7.00.[65,66] The differential diagnosis can be narrowed further by assessing the cellular predominance. With a pH < 7.30 and neutrophil predominance, the differential diagnosis includes acute lupus pleuritis, cholesterol pleural effusion, complicated parapneumonic effusion, empyema and oesophageal rupture.[65,66] When the pH is <7.30 with a mononuclear cell predominance, the clinician should consider chronic rheumatoid pleural effusion, malignancy or tuberculous pleural effusion. When the pH is <7.30 with eosinophilia, paragonimiasis or another parasitic infection is likely to be the cause. When the pH is measured using a blood gas analyzer, lidocaine and heparin must be utilized appropriately to ensure an accurate measurement.[67]

LOW PLEURAL FLUID GLUCOSE CONCENTRATION

Exudates with a low pleural fluid glucose concentration (<600 mg/L) or, more precisely, a pleural fluid to serum glucose ratio of <0.50, are associated with the same diagnoses as low pleural fluid pH (Table 9).[68,69] There are only three clinical scenarios in which the pleural fluid glucose concentration is zero; these are chronic rheumatoid pleurisy, empyema and paragonimiasis.[67] When the pleural fluid/serum glucose ratio is substantially >1.0, oesophageal rupture with continuing oral glucose intake, extravascular migration of a central venous catheter with glucose infusion and peritoneal dialysis should be considered as possible causes.[3]

PLEURAL FLUID AMYLASE

The only indication for measuring pleural fluid amylase is when pancreatic disease, oesophageal rupture or malignancy is being considered.[70–72] The definition of elevated pleural fluid amylase is a level greater than the upper limits of normal serum amylase and a pleural fluid to serum ratio >1.0. In cases of pancreaticopleural fistula, amylase levels may exceed 100 000 IU/L. In patients with high levels of salivary amylase, the differential diagnosis is oesophageal rupture or adenocarcinoma.[71,72]

BIOMARKERS

Biomarkers are proteins in tissues, serum and other body fluids that have been utilized in the diagnosis and prognosis of disease states in the setting of malignancy. Biomarkers, such as carcinoembryonic antigen, neuron-specific enolase, CA 125, CA 19-9, α-fetoprotein, CYFRA 21-1 and osteopontin, have been used to discriminate between malignant and benign pleural exudates. While the presence of high levels of these biomarkers may suggest malignancy, biomarker levels are not diagnostic when the increases are modest.[73–75] Patients with infections, pulmonary emboli and malignancies may have elevated levels of fibrin degradation products in the pleural fluid.[76] High levels of adenosine deaminase, particularly isoenzyme 2 (ADA2), lysozyme and interferon-γ are present in tuberculous pleurisy pleural effusions.[77,78] Soluble mesothelin-related protein (SMRP) shows potential as a promising diagnostic biomarker for malignant mesothelioma. SMRP may also be useful for monitoring treatment outcomes.[79–81]

Currently, the most frequently used biomarker for pleural disease is brain natriuretic peptide (BNP), and N-terminal (NT)-pro BNP. In patients with suspected heart failure, high levels of BNP and NT-pro BNP in both serum and pleural fluid confirm the diagnosis of CHF-related pleural effusions.[82] Both natriuretic peptides are secreted almost exclusively from the ventricles, in response to pressure and volume overload. Patients with BNP levels <100 pg/mL or NT-pro BNP levels <400 pg/mL are unlikely to have CHF. Patients with BNP levels >400 pg/mL and NT-pro BNP levels >2000 pg/mL are highly likely to have CHF.[83]

SUMMARY

The diagnostic sensitivity of thoracentesis is substantially increased if a detailed history is obtained, appropriate laboratory tests are evaluated, chest

Table 9 Exudates with low pleural fluid glucose (<600 mg/L or pleural fluid/serum glucose <0.50) (Data taken from Sahn[4])

	Glucose range (mg/L)	~Incidence %
• Complicated parapneumonic effusion/empyema ($n \geq 200$)	0–400	100
• Chronic rheumatoid pleurisy ($n = 30$)	0–300	100
• Paragonimiasis (n unknown)	0–110	Unknown
• Oesophageal rupture ($n = 15$)	150–600	100
• Malignancy ($n = 175$)	300–590	15
• Tuberculous pleurisy ($n = 30$)	300–590	15
• Acute lupus pleuritis ($n = 25$)	300–590	15

imaging findings are reviewed and a differential diagnosis is established prior to PFA. The diagnosis of a transudative effusion confirms an imbalance in hydrostatic and oncotic pressures, normal pleura and a limited differential diagnosis that is typically apparent from the clinical presentation. Exudates are the result of infections, malignancies, inflammation, impaired lymphatic drainage or the effects of drugs, and pose a greater diagnostic challenge. The differential diagnosis for an exudative effusion can be narrowed if the pleural fluid LDH level exceeds 1000 IU/L, if it contains ≥80% lymphocytes, if the pleural fluid ph is <7.30 or if there is pleural eosinophilia of >10%.

REFERENCES

1 Davies J. Development of the respiratory system. In: Davies J (ed.) *Human Developmental Anatomy*. Ronald Press, New York, 1963; 135–43.
2 Wang NS. Anatomy of the pleura. *Clin. Chest Med.* 1998; **19**: 229–40.
3 Sahn SA. Pleural effusions of extravascular origin. *Clin. Chest Med.* 2006; **27**: 285–308.
4 Sahn SA. Diagnostic value of pleural fluid analysis. *Semin. Respir. Crit. Care Med*. 1995; **16**: 269–78.
5 Cohen M, Sahn SA. Resolution of pleural effusions. *Chest* 2001; **119**: 1547–62.
6 Heidecker J, Sahn SA. The spectrum of pleural effusions after coronary artery bypass grafting surgery. *Clin. Chest Med.* 2006; **27**: 267–84.
7 Epler GR, McLoud TC, Gaensler EA. Prevalence and incidence of benign asbestos pleural effusion in a working population. *JAMA* 1982; **247**: 617–22.
8 Kilburn CD, McKinsey DS. Recurrent massive pleural effusion due to pleural, pericardial, and epicardial fibrosis in histoplasmosis. *Chest* 1991; **100**: 1715–17.
9 Lonky SA, Catanzaro A, Moser KM *et al*. Acute coccidioidal pleural effusion. *Am. Rev. Respir. Dis.* 1976; **114**: 681–8.
10 Sahn SA. Pleural disease induced by drugs. In: Camus P, Rosenow EC (eds) *Drug Induced and Iatrogenic Respiratory Disease*. Hodder A, UK, 2011; 284–96.
11 Huggins JT, Doelken P, Gurung P *et al*. The prevalence of lung entrapment in patients with malignant pleural effusions. *Am. J. Respir. Crit. Care Med.* 2009; **179**: A4478.
12 Mattison L, Coppage L, Alderman D *et al*. Pleural effusions in the medical intensive care unit: prevalence, causes, and clinical implications. *Chest* 1997; **111**: 1018–23.
13 Eid AA, Keddissi JJ, Kinasewitz GT. Hypoalbuminemia as a cause of pleural effusions. *Chest* 1999; **115**: 1066–9.
14 Grefberg N, Danielson B, Benson L *et al*. Right-sided hydrothorax complicating peritoneal dialysis. *Nephron* 1983; **34**: 130–4.
15 Lepage S, Bisson G, Verreault J *et al*. Massive hydrothorax complicating peritoneal dialysis. Isotopic investigation. *Clin. Nucl. Med.* 1993; **18**: 849–901.
16 Nomoto Y, Suga T, Nakajima K *et al*. Acute hydrothorax in continuous, ambulatory, peritoneal dialysis – a collaborative study of 161 centers. *Am. J. Nephrol.* 1989; **9**: 363–7.
17 Walker WC, Wright V. Rheumatoid pleuritis. *Ann. Rheum. Dis.* 1967; **26**: 467–74.
18 Sahn SA, Iseman M. Tuberculous empyema. In: Hefner JE, Sahn SA (eds) *Diagnosis and Management of Empyema. Seminars in Respiratory Infection*. Vol. **14**. WB Saunders Company, Philadelphia, PA, 1999; 82–7.
19 Nordkild P, Kromann-Andersen H, Struve-Christensen E. Yellow nail syndrome – the triad of yellow nails, lymphedema, and pleural effusions. A review of the literature and a case report. *Acta Med. Scand.* 1986; **219**: 221–7.
20 Sahn SA. Approach to patients with pleural diseases. In: Light RW, Lee YCG (eds) *Textbook of Pleural Diseases*, 2nd edn. Hodder Arnold, UK, 2008; 201–26.
21 Singer JA, Kaplan MM, Katz RL. Cirrhotic pleural effusion in the absence of ascites. *Gastroenterology* 1977; **73**: 575–7.
22 Cavina G, Vichi G. Radiological aspects of pleural effusions in medical nephropathy in children. *Ann. Radiol. Diagn. (Bologna)* 1958; **31**: 163–202.
23 Stark DD, Shanes JG, Baron RL *et al*. Biochemical features of urinothorax. *Arch. Intern. Med.* 1982; **142**: 1509–11.
24 Kaye MD. Pleuropulmonary complications of pancreatitis. *Thorax* 1968; **23**: 297–306.
25 Anderson WJ, Skinner DB, Zuidema GD *et al*. A chronic pancreatic pleural effusion. *Surg. Gynecol. Obstet.* 1973; **137**: 827–30.
26 Press OW, Press NO, Kaufman SD. Evaluation and management of chylous ascites. *Ann. Intern. Med.* 1982; **96**: 358–64.
27 Majzlin G, Stevens FL. Meigs' syndrome. Case report and review of literature. *J. Int. Coll. Surg.* 1964; **42**: 625–30.
28 De Cosse JJ, Poulin TL, Fox PF *et al*. Subphrenic abscess. *Surg. Gynecol. Obstet.* 1974; **138**: 841–6.
29 Maher GG, Berger HW. Massive pleural effusions: malignant and non-malignant causes in 46 patients. *Am. Rev. Respir. Dis.* 1972; **105**: 458–60.
30 Blackman NS, Rabin CB. Bilateral pleural effusion; its significance in association with a heart of normal size. *J. Mt. Sinai Hosp. N.Y.* 1957; **24**: 45–53.
31 Maguire R, Fauci AS, Doppman JL *et al*. Unusual radiographic features of Wegener's granulomatosis. *AJR Am. J. Roentgenol.* 1978; **130**: 233–8.
32 Carr DT, Mayne JG. Pleurisy with effusion in rheumatoid arthritis with reference to the low concentration of glucose in pleural fluid. *Am. Rev. Respir. Dis.* 1962; **85**: 345–50.
33 Gumbs RV, McCauley DI. Hilar and mediastinal adenopathy in septic pulmonary embolic disease. *Radiology* 1982; **142**: 313–15.
34 Rubin SA. Radiographic spectrum of pleuropulmonary tularemia. *AJR Am. J. Roentgenol.* 1978; **131**: 277–81.
35 Fine NL, Smith LR, Sheedy PF. Frequency of pleural effusions in mycoplasma and viral pneumonias. *N. Engl. J. Med.* 1970; **283**: 790–3.
36 Almoosa KF, McCormack FX, Sahn SA. Pleural disease in lymphangioleiomyomatosis. *Clin. Chest Med.* 2006; **27**: 355–68.
37 Horowitz ML, Schiff M, Samuels JL. Pneumocystis carinii pleural effusion pathogenesis, and pleural fluid analysis. *Am. Rev. Respir. Dis.* 1993; **148**: 232–4.
38 Huggins JT, Doelken P, Sahn SA *et al*. Pleural effusions in a series of 181 outpatients with sarcoidosis. *Chest* 2006; **129**: 1599–604.
39 Janower ML, Vlennerhassett JD. Lymphangitic spread of metastatic cancer to the lung: a radiologic-pathologic classification. *Radiology* 1971; **101**: 267–73.
40 Bynum LJ, Wilson JE III. Radiographic features of pleural effusions in pulmonary embolism. *Am. Rev. Respir. Dis.* 1978; **117**: 829–34.
41 Agrawal V, Sahn SA. Lipid pleural effusions. *Am. J. Med. Sci.* 2008; **335**: 16–20.
42 Hunder GG, McDuffie FC, Hepper NG. Pleural fluid compliment in systemic lupus erythematosis and rheumatoid arthritis. *Ann. Intern. Med.* 1972; **76**: 357–63.
43 Chiles C, Guthaner DF, Jamieson SW. Heart-lung transplantation: the post operative chest radiograph. *Radiology* 1985; **154**: 299–304.
44 Sharma OP, Gordonson J. Pleural effusion in sarcoidosis: a report of six cases. *Thorax* 1975; **20**: 95–101.
45 Roper WH, Waring JJ. Primary serofibrinous pleural effusion in military personnel. *Am. Rev. Respir. Dis.* 1955; **71**: 616–34.
46 Berger HW, Rammohan G, Neff MS *et al*. Uremic pleural effusion. A study in 14 patients on chronic dialysis. *Ann. Intern. Med.* 1975; **82**: 362–4.

47 Huggins JT, Sahn SA, Heidecker J *et al*. Characteristics of trapped lung, pleural fluid analysis, manometry, and air-contrast chest computed tomography. *Chest* 2007; **131**: 206–13.
48 Sahn SA. Approach to patients with pleural diseases. In: Light RW, Lee YCG (eds) *Textbook of Pleural Diseases*, 2nd edn. Hodder Arnold, UK, 2008; 201–8.
49 Huggins JT. Chylothorax and cholesterol pleural effusion. *Semin. Respir. Crit. Care Med.* 2010; **31**: 743–50.
50 Strange C, Allan ML, Freedland PN *et al*. Biliopleural fistula as a complication of percutaneous biliary drainage: experimental evidence for pleural inflammation. *Am. Rev. Respir. Dis.* 1988; **137**: 959–61.
51 Huggins JT, Sahn SA. Duro-pleural fistula diagnosed by beta II-transferrin. *Respiration* 2003; **70**: 423–5.
52 Nosanchuck JS, Naylor B. A unique cytologic picture in pleural fluid from patients with rheumatoid arthritis. *Am. J. Clin. Pathol.* 1968; **50**: 330–5.
53 Sahn SA. State of the art. The Pleura. *Am. Rev. Respir. Dis.* 1988; **138**: 184–234.
54 Heffner JE. Discriminating between transudates and exudates. *Clin. Chest Med.* 2006; **27**: 241–52.
55 Porcel JM. Pleural effusions from congestive heart failure. *Semin. Respir. Crit. Care Med.* 2010; **31**: 689–97.
56 Light RW, MacGregor I, Luchsinger PC *et al*. Pleural effusion: the diagnostic separation of transudates and exudates. *Ann. Intern. Med.* 1972; **77**: 507–13.
57 Rodriguez JN, Pereira A, Martinez JC *et al*. Pleural effusion in myeloma. *Chest* 1994; **105**: 622–4.
58 Winterbauer RH, Riggins RCK, Griesman FA *et al*. Pleuropulmonary manifestations of Waldenstrom's macroglobulinemia. *Chest* 1974; **66**: 368–75.
59 Sahn SA, Heffner JE. Pleural fluid analysis. In: Light RW, Lee YCG (eds) *Textbook of Pleural Diseases*. Hodder A, UK, 2008; 209–26.
60 Light RW, Erozan YS, Ball WC Jr. Cells in pleural fluid. Their value in differential diagnosis. *Arch. Intern. Med.* 1973; **132**: 854–60.
61 Nakamura Y, Ozaki P, Kamei T *et al*. Factors that stimulate the proliferation and survival of eosinophils in eosinophilic pleural effusion: relationship to granulocyte/macrophage colony-stimulating factor, interleukin-5, and interleukin-3. *Am. J. Respir. Cell Mol. Biol.* 1993; **8**: 605–11.
62 Rubins JB, Rubins HB. Biology and prognostic significance of eosinophilic pleural effusion: a prospective study. *Chest* 1996; **110**: 1271–4.
63 Martinez-Garcia MA, Cases-Viedma E, Cordero-Rodriguez PJ *et al*. Diagnostic utility of eosinophils in pleural fluid. *Eur. Respir. J.* 2000; **15**: 166–9.
64 Askin FB, McCann BG, Kuhn C. Reactive eosinophilic pleuritis: a lesion to be distinguished from pulmonary eosinophilic granuloma. *Arch. Pathol. Lab. Med.* 1977; **101**: 187–91.
65 Good JT, Taryle DA, Maulitz RM *et al*. Diagnostic value of pleural fluid pH. *Chest* 1980; **78**: 55–9.
66 Sahn SA. Pleural fluid pH in the normal state and in diseases affecting the pleura. In: Chretien J, Bignon J, Hirsch A (eds) *The Pleura in Health and Disease*. Marcel Dekker, New York, 1985; 253–66.
67 Rahman NM, Mishra EK, Davies HE *et al*. Clinically important factors influencing the diagnostic measurement of pleural fluid pH and glucose. *Am. J. Respir. Crit. Care Med.* 2008; **178**: 483–90.
68 Rodriguez-Panadero F, Lopez Mejin J. Low glucose and pH levels in malignant pleural effusions. Diagnostic significance and prognostic value in respect to pleurodesis. *Am. Rev. Respir. Dis.* 1989; **139**: 663–7.
69 Sahn SA. Pathogenesis: clinical features of diseases associated with a low pleural fluid glucose. In: Chretien J, Bignon J, Hirsch A (eds) *The Pleura in Health and Disease*. Marcel Dekker, New York, 1985; 267–82.
70 Joseph J, Viney S, Beck P *et al*. A prospective study of amylase-rich pleural effusions with special reference to the amylase isoenzyme analysis. *Chest* 1992; **102**: 1455–9.
71 Kramer MR, Sepero RJ, Pitchenik AE. High amylase levels in neoplasm-related pleural effusion. *Ann. Intern. Med.* 1989; **110**: 567–9.
72 Triggiani E, Belsey R. Oesophageal trauma: incidence, diagnosis, and management. *Thorax* 1977; **32**: 241–99.
73 Burgess L, Burgess U. Biochemical analysis of pleural, peritoneal, and pericardial effusions. *Clin. Chim. Acta* 2004; **343**: 61–84.
74 Marel M, Stastny B, Melinova L *et al*. Diagnosis of pleural effusions: experience with clinical studies, 1986–1990. *Chest* 1995; **107**: 1598–603.
75 San Jose ME, Alvarez D, Valdes L *et al*. Utility of tumour markers in the diagnosis of neoplastic pleural effusion. *Clin. Chim. Acta* 1997; **265**: 193–205.
76 Raga OG, Casson IF. Fibrinogen degradation products in pleural effusions. *Br. J. Dis. Chest* 1980; **74**: 164–8.
77 Ungerer JP, Oosthuizen HM, Retief JH *et al*. Significance of adenosine deaminase activity and its isoenzymes in tuberculous effusions. *Chest* 1994; **106**: 33–7.
78 Valdes L, Alvarez D, San Jose E *et al*. Value of adenosine deaminase in the diagnosis of tuberculous pleural effusions in young patients in a region of high prevalence of tuberculosis. *Thorax* 1995; **50**: 600–3.
79 Scherpereel A, Grigoriu B, Conti M *et al*. Soluble mesothelium-related peptides in the diagnosis of malignant pleural mesothelioma. *Am. J. Respir. Crit. Care Med.* 2006; **173**: 1155–60.
80 Robinson BW, Creaney J, Lake R *et al*. Mesothelin-family proteins and diagnosis of mesothelioma. *Lancet* 2003; **362**: 1612–16.
81 Davies HD, Sadler RS, Bielsa S *et al*. Clinical impact and reliability of pleural fluid mesothelin in undiagnosed pleural effusions. *Am. J. Respir. Crit. Care Med.* 2009; **180**: 437–44.
82 Porcel JM, Martinez-Alonso M, Cao G *et al*. Biomarkers of heart failure in pleural fluid. *Chest* 2009; **136**: 671–7.
83 Dickstein K, Cohen-Solal A, Filippatos G *et al*. Task force for diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* 2008; **29**: 2388–442.