Management of Pleural Effusions in Acute Medical Settings: a practical guide

Dr Y C Gary Lee & Dr R J O Davies

Abstract

In the setting of acute medical care, pleural effusions are often overlooked. This article aims to provide a practical guide for the initial workup of pleural effusions and the management of common types of effusions.

Key Words

Pleural Effusion; Thoracentesis; Malignant Effusion; Parapneumonic Effusion; Pleural Biopsy.

Key Points

1. Prompt recognition and management of pleural effusions may reduce morbidity and mortality.
2. The diagnosis of a pleural effusion is usually confirmed with radiographs or ultrasonography.
3. Appropriate pleural fluid analysis enables categorisation into transudates or exudates. Parapneumonic, malignant and tuberculous effusions are the commonest types of exudative effusions, whereas congestive heart failure accounts for most transudates.
4. Early referral to a specialist respiratory unit is recommended if the effusion remains undiagnosed after the initial workup, if atypical radiological or biochemical features exist, or if the patient is unwell.

Introduction

Pleural effusion is common in clinical practice and, extrapolating from European data, affects over 180000 people in the United Kingdom each year.[1] Pleural disease can complicate a wide range of pulmonary and systemic disorders, so that establishing the underlying cause of a pleural effusion can be a challenge. Delay to management of pleural effusions can contribute to morbidity, and in some cases leads to significant complications. Detailed discussion on pleural effusion management can be found in the British Thoracic Society guidelines on pleural disease.[2-4]

Pathophysiology

Pleural effusions develop when the rate of pleural fluid formation exceeds that of its drainage. Transudative effusions accumulate from imbalances in hydrostatic and oncotic pressures, while exudates often result from pleural inflammation, lymphatic disruptions or malignancy.[5]

Clinical Features

Patients with pleural effusions can be asymptomatic, but may also present with dyspnoea. Dyspnoea usually results more from altered diaphragmatic and chest wall mechanics than compression of the lung. Pathologies of the underlying lung can also contribute to breathlessness. Pleuritic chest pain can occur in patients with a pleural effusion as a result of inflammation of the parietal pleura.

The textbook clinical signs of pleural effusion – 'stony' dullness on percussion, decreased fremitus and reduced breath sounds - are usually present only when the effusion exceeds 500mL in volume. It must be remembered that an elevated hemi-diaphragm will produce similar clinical signs.

Recognising a Pleural Effusion

In everyday clinical practice, pleural effusions are commonly first diagnosed on chest radiographs. In most cases, radiological recognition is straightforward (see figure 1a). However, detecting (and estimating the size) of pleural effusions on radiographs in the presence of atelectasis or consolidation is often difficult. Small pleural effusions which blunt the costophrenic angle are not readily distinguishable from pleural thickening (see figure 1b). Likewise, subpulmonic effusions can easily be mistaken for an elevated hemi-diaphragm. (See Davies and Gleeson for review on radiology of pleural disease).[6]

The easy availability and high sensitivity of ultrasound scanning has made it the best radiological modality to identify and locate small pleural effusions for aspiration (thoracentesis).[7] The safety of ultrasound-guided thoracentesis,[8] and its superiority over bedside determination of sites for pleural puncture[9] have been shown recently in large observational studies. Decubitus radiographs, traditionally used to detect small pleural effusions,[10] now have little role.

Dr Y C Gary Lee
MBChB PhD FCCP FRACP
Wellcome Trust Centre for Human Genetics, Oxford, U.K.

Dr Lee is the recipient of a Wellcome Trust-New Zealand Health Research Council Research Fellowship and a Graham Aitken Nuffield Medical Postgraduate Travelling Scholarship.

Dr Robert J O Davies
DM FRCP
Oxford Pleural Disease Unit, Oxford Centre for Respiratory Medicine
Oxford Radcliffe Hospital
Oxford, U.K.

Correspondence:
Dr Y C Gary Lee,
Centre for Respiratory Research,
University College London
5 University Street,
London, U.K.
WC1E 6JJ
Tel: 0207 6796976
Fax: 0207 6796973
E-mail:ycgarylee@hotmail.com

Management of Pleural Effusions in Acute Medical Settings: a practical guide

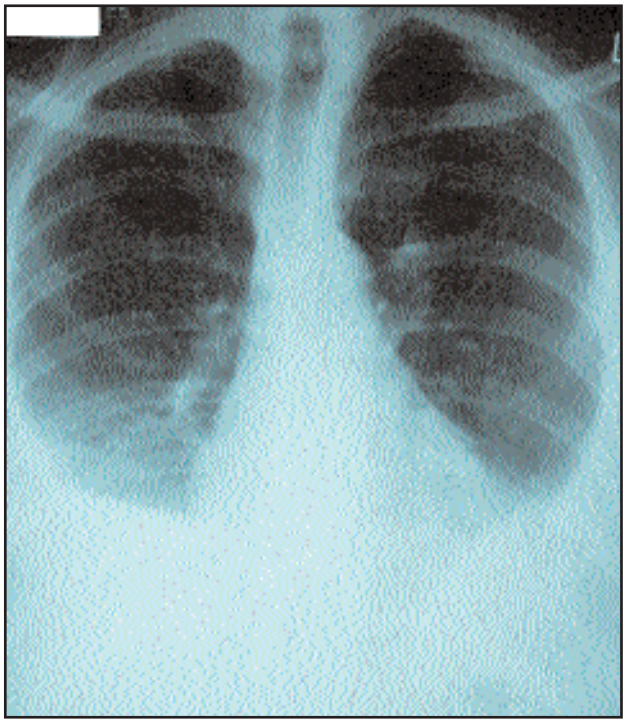

Fig 1a. A chest radiograph of a patient 6 weeks after his coronary artery bypass surgery (CABG)-notice the sternotomy wires- showing bilateral pleural effusions. The temporal relationship of the effusion and fluid analysis were compatible with a post-CABG effusion

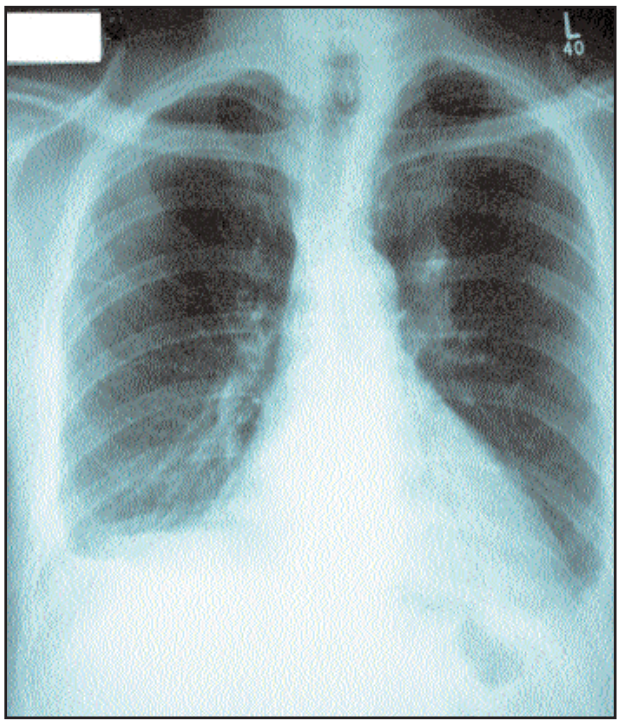

Fig 1b. The chest radiograph of the same patient at 6 months post-CABG, showing mild bilateral residual pleural thickening

Investigating the underlying cause of pleural effusions

The range of aetiology of pleural effusions is wide (see Table 1). At least 50 causes of exudative effusions have been documented.[5] Determining the cause of an effusion requires a detail clinical history and conduction of the appropriate fluid analysis. The aim is to establish a diagnosis promptly while keeping the number of pleural interventions to a minimum. This is particularly important as the incidence of malignant mesothelioma is rising significantly in the UK[11] and needle tract metastases occur in 40% of previous pleural puncture sites in mesothelioma patients.[12]

Clinical History

Good history taking is essential. For example, a bilateral effusion in a patient with cardiac disease, dyspnoea and orthopnoea would raise a strong suspicion of transudative effusion from congestive heart failure. A history of recent trauma may suggest a haemothorax. Occupational exposure to asbestos, even from the distant past, can be relevant. Importantly, the presence of infective or septic symptoms may be indicative of an empyema, which requires prompt drainage.

Thoracentesis

Pleural fluid analysis can provide information that supports or confirms the clinical diagnosis in the majority of cases. While thoracentesis is generally safe, complications can and do occur. Informed consent should be obtained. There are few absolute contraindications; however patients with a coagulopathy and those with underlying cystic lung diseases are obviously at higher risk of bleeding or pneumothorax following the procedure.

While thoracentesis can usually be performed at the bedside, we recommend that image-guided thoracentesis be used with a low threshold, especially in cases where the effusion is small and/or loculated, if the radiological features are atypical, and in high-risk patients (eg those with poor lung reserve). Alternatively, the optimal site of fluid aspiration can be identified using ultrasound for bedside thoracentesis. The marked site is only valid if the patient is placed in the same position (eg sitting upright leaning forward) as when the ultrasound is performed.

Premedication is generally not required. In a recent retrospective study of 941 thoracentesis procedures without premedication, only 0.6% of patients experienced a vasovagal reaction, all of whom where successfully treated with atropine.[8] Midazolam or atropine can be administered according to the clinicians' judgement for very anxious patients. Potential complications include vasovagal syncope, bleeding or infection. Pneumothorax can develop from lung puncture, but may represent trapped lungs (thickened visceral pleura or endobronchial obstruction inhibiting full lung expansion) rather than air-leakage. The techniques for thoracentesis are covered elsewhere.[13]

There is no strict rule for the maximum volume of fluid that can be removed at one time. Complete drainage of the effusion can provide more symptomatic relief and may also improve diagnostic yield. However, evacuation of a large volume of fluid (eg >1L) can lead to re-expansion pulmonary oedema. Most patients develop a cough (± chest pain) after the removal of large quantity of

Transudates

Common

- Congestive heart failure
- Hepatic cirrhosis
- Nephrotic syndrome
- Hypoalbuminemia from other causes

Uncommon

- Constrictive pericarditis
- Peritoneal dialysis
- Effusions secondary to trapped lungs
- Superior vena caval obstruction

Exudates

Common

- Parapneumonic effusions
- Malignancy
- TB pleuritis
- Pulmonary embolism
- Secondary to sub-diaphragmatic inflammation (eg hepatic abscess)
- Rheumatological (esp Rheumatoid arthritis, SLE)
- Pancreatitic (acute pancreatitis; pancreatic pseudocyst)
- Haemothorax (eg traumatic)

Uncommon

- Drug-induced
- Lymphatic disruption (Chylothorax, yellow nail syndrome)
- Oesophageal perforation
- Misplacement of central venous cathether
- Sarcoidosis
- Bengin asbestos pleural effusion
- Hypothyroidism
- Ovarian hyperstimulation syndrome
- Post-irradiation
- Fungal/Parasitic infection
- Meig's syndrome

Table 1. Causes of Plaural Effusions (modified from Sahn and Heffner).[28]

pleural fluid, at which time the procedure should be discontinued. Measurement of elastance has been used as a guide for fluid removal,[14] but is not readily available in most centres.

Closed Pleural Biopsy

Closed pleural biopsy, eg with Abram's or Cope's needles, is routinely employed in some centres for investigation of pleural effusions.[13] However, potential additional benefits from closed needle biopsy are diminishing with advancements in laboratory diagnostic techniques. With progress in immunohistochemistry, the additional sensitivity of closed pleural biopsy over pleural fluid cytology for malignant pleural effusion is likely to be small. In addition, CT-guided cutting needle biopsy is significantly more useful than blind pleural biopsy, especially if pleural abnormalities are seen on CT.[15]

In regions where TB pleuritis is endemic, closed pleural biopsy, which has a higher yield than pleural fluid culture, may still be justified. The yield is increased if at least 4 samples are taken[16] and the biopsies should be placed in 10% formaldehyde for histological examination and sterile saline for tuberculosis culture. In one review of 2893 pleural biopsies, the diagnostic yield was 75% for tuberculosis and 57% for carcinoma.[17] Complications of pleural biopsy include local pain (1-15%), pneumothorax (3-15%), vasovagal reaction (1-5%), haemothorax (<2%), haematoma (<1%) and transient fever (<1%) and very rarely death secondary to haemorrhage.[17-19] Closed pleural biopsy should be performed only by, or under the supervision of, medical officers of adequate experience in this procedure. Detail discussion on the role of closed pleural biopsy can be found elsewhere.[10]

Newer modalities such as pleural fluid adenosine deaminase (ADA),[20,21] PCR for mycobacteria[22] and interferon measurements[23] are under investigation as diagnostic tests for TB pleuritis. Pleural fluid ADA is now routinely performed in many TB endemic countries, further minimising any need for closed pleural biopsy.

Pleural Fluid Analysis

• *Appearance:* Visual inspection of the pleural fluid may provide important clues to its aetiology.[10] For example, pus aspirated from the pleural space provides an immediate diagnosis of empyema. Chylothorax (accumulation of lymph in the pleural space) has a characteristic milky appearance. Most pleural fluids are straw-coloured, but blood-staining is common, and does not necessarily indicate a haemothorax. Urinothorax (urine accumulation in the pleural space from renal tract fistulae) is a rare diagnosis can be made readily from the smell of the pleural aspirate.

• *Transudate vs Exudate:* The distinction between a transudate and an exudate is crucial. Light's criteria[24] (see Table 2) have been used for 30 years and remain the practical standard. Many other biochemical parameters (eg pleural fluid cholesterol levels) have been proposed, but none were superior.[25] Recently, it has been suggested that instead of a single cut-off (dichotomy) as in Light's criteria, the use of multi-level or continuous likelihood ratios of protein and LDH may improve the predictive values.[26]

Pleural fluid should therefore be sent for protein and lactate dehydrogenase (LDH) measurements routinely. If the pleural fluid is a transudate, additional tests are not needed, unless the diagnosis is not in keeping with the clinical picture.

• *Pleural Fluid White Blood Cell Counts:* For exudates, additional tests on the pleural fluid will provide helpful information.[27] Differential pleural fluid white cell counts can help direct investigations. Neutrophilic pleural fluids suggests intense pleural inflammation, and are commonly associated with parapneumonic infection/empyema, pulmonary emboli, pancreatic effusions and malignancy.[10] Lymphocytic (lymphocyte >50% of total leukocytes) pleural fluid suggests TB, malignancy, post-coronary

artery bypass (CABG) effusion, chronic rheumatoid pleuritis or lymphatic disruption (lymphoma, chylothorax, yellow nail syndrome).[28] Eosinophilic (eosinophils >10% of total leukocytes) pleural effusions are not uncommon, and are secondary usually to blood or air in the pleural space,[29] although also seen in post-CABG pleural effusions,[30] benign asbestos pleural effusions,[31] parasitic/fungal infections and allergic reactions.[10, 28]

- A pleural effusion is an exudate if any of the following criteria is met:

1. Pleural fluid to serum protein ratio >0.5
2. Pleural fluid to serum LDH >0.6
3. Pleural fluid LDH > 2/3 of the upper limit of normal serum LDH

- A pleural effusion is a transudate if it meets none of the above criteria.

Table 2. Light's Criteria [24]

• *pH and glucose:* pH and glucose in the pleural fluid reflect the metabolic activities in the pleural cavity, and/or altered transfer of protons and glucose across the pleura.[28] Decreases in both parameters are commonly seen in infected pleural fluid (eg empyema, TB) and in other pleural inflammatory conditions (eg rheumatoid pleuritis). In malignant effusions, low pH may be a crude reflection of high tumour load in the pleural cavity.[32] Low pleural fluid pH statistically predicts lower success rate for pleurodesis,[33] but the accuracy of prediction is insufficient to warrant its use as a guide for patient selection.

• *Bacterial and Mycobacterial Culture:* If clinically appropriate, fluid should be sent for Gram staining and culture for bacteria and mycobacteria.[27] Pleural fluid should be directly inoculated into aerobic and anaerobic culture bottles.[34] Preparing cell-blocks from concentrating the cells in the pleural fluid can increase the yield of Gram staining. Negative culture results however do not exclude empyema or TB pleuritis.

• *Cytology:* Exudative pleural fluids should be sent for cytological examination. Positive diagnostic rate of malignant effusion by cytology depends on various factors. In early stage pleural tumours, the number of malignant cells in the pleural fluid may be low and diagnosis is more difficult. The diagnostic yield also depends on the type of tumour (mesothelioma, for example, is more difficult to diagnose on cytology) and the experience of the cytologist.

One study revealed no relationship between the volume of pleural fluid sent and the likelihood of a positive diagnosis of malignant effusion.[35] This result has yet to be confirmed by other studies. Since the pleural fluid is otherwise discarded, it remains sensible to send as much of the aspirate to the cytologist as possible.

• *Others:* Specific parameters should be tested for when clinically indicated. A small amount of blood in the pleural fluid can make it appear 'bloody', but a true haemothorax is one in which the haematocrit is 50% (or above) that of the peripheral blood.[28]

High pleural fluid amylase can occur with oesophageal rupture, in effusions due to pancreatic causes (eg from pancreatic pseudocysts), and in about 10% of malignant pleural effusions, (especially adenocarcinomas).[28] However, routine measurements of pleural fluid amylase is not indicated.[36, 37] Triglyceride and cholesterol levels should be measured if chylothorax and pseudochylothorax are suspected.[38] Flow cytometry is very useful to diagnose or exclude lymphoma in effusions that are predominantly lymphocytic. Tumour markers[10] and cytokine levels[39] in pleural fluid, while extensively investigated, are neither sensitive nor specific enough for diagnostic purposes at present.

Management of common types of pleural effusions

Congestive Heart Failure (CHF)

In the general medical wards, CHF is the most common cause of pleural effusions. About 50-75% of patients admitted with CHF will have a pleural effusion on radiographs.[40, 41] The incidence increases to 87% if CT scanning is used.[42] A compatible clinical history and a transudative effusion would secure the diagnosis. The effusions are commonly bilateral.[43] Occasionally, pleural effusions from CHF may appear as 'exudates' on biochemical criteria, especially in patients who are on diuretics. This is postulated, though never proven, to be a result of differential drainage of fluid over the protein molecules from the pleural space due to diuretic therapy. In such cases, it may be useful to calculate the albumin gradient (AG), using the formula: AG = plasma albumin – pleural fluid albumin. A gradient of >1.2g/dL indicates that the effusion was formed as a transudate.[43]

Experimental studies have shown that the pleural fluid in CHF originates from interstitial fluid of the lung.[44] The pleural space thus provides an escape route for pulmonary oedema. Management of the underlying CHF should control symptoms. If the effusion is large, drainage of the fluid may help to improve dyspnoea.[43] Pleurodesis may be helpful for rapidly recurrent CHF effusions,[45] but is not usually encouraged.

Most patients with CHF are elderly and, in the occasional cases, have alternate causes for their pleural effusions, eg malignancy. If the effusion does not resolve with aggressive diuresis, or if atypical radiological or biochemical features exist, further investigations are necessary to exclude alternative or concurrent aetiologies.

Parapneumonic Effusions and Empyema

Up to 50% of patients with pneumonia will develop a pleural effusion.[46] Parapneumonic effusions must be recognised and managed appropriately and promptly, to avoid development into empyema, which is associated with significant morbidity and mortality (up to 20%).[47] Hence, rapid drainage, as implied by the phrase 'the sun should never set on a parapneumonic effusion' is appropriate.[48]

Patients who present with pneumonia and a pleural effusion must be investigated promptly.[49] The effusion should be aspirated, preferably to dryness, either by thoracentesis or chest tube drainage.[50] This, together with adequate antibiotics therapy, is usually sufficient to avoid any further need for pleural interventions. Likewise, patients with clinical or radiological diagnosis of pneumonia should have radiological follow-up to ensure no subsequent accumulation of a parapneumonic effusion, even if there was no effusion at the time of admission.

The appropriate antibiotic regimen depends on the local pattern of bacterial resistance, and can be refined according to sensitivity results if bacterial culture is positive. Mixed organism infections are not uncommon, especially if E Coli is present in the bacterial fluid.[10]

Empyemas are often loculated with high fibrinous contents, which makes complete drainage difficult. Prompt chest tube insertion, preferably with image guidance (eg by ultrasound or CT scanning) is recommended.[47] Fibrinolytics are commonly used to enhance the breakdown of fibrin septa of the loculations to allow complete evacuation of the infected fluid.[51-54] Streptokinase, 250000 units twice daily, administered intrapleurally via the chest tube, is commonly used. If there is no objective improvement in fever, inflammatory markers (eg leukocyte count, C-reactive protein) and size of the effusion on radiographs after 48 or 72 hours, referral for surgical drainage should be considered. Video-assisted thoracoscopic surgery (VATS) should be the first line approach; thoracotomy, which carries higher complications, should be reserved for cases where VATS is not technically feasible.[47]

Malignant Pleural Effusions (MPE)

Malignant pleural effusions accounted for 22% of all pleural effusions in a community study in Europe.[1] Considerable numbers of patients with primary breast and lung carcinomas (50% and 25% respectively) will develop a pleural effusion.[55] Mesothelioma is also an endemic disease, with 250,000 deaths expected in Western Europe over the next 35 years.[56] Over 90% of patients with pleural mesothelioma present with a pleural effusion.[57] In up to 20% of patients with MPE, pleural effusion is the first presentation of malignancy.

If malignancy is suspected, several approaches can be taken. The fluid can be drained and sent for analysis. If the initial workup is negative, the patient can be followed up over the next few weeks to assess for fluid re-accumulation. If the effusion recurs, further thoracentesis (± pleural biopsy), along with CT scanning, should be performed. Alternatively, thoracoscopy facilities may be used to obtain pleural biopsy under direct vision. In cases where pleural abnormalities are identifiable on CT scans, CT-guided biopsy is a useful alternative.[60]

The most common cytological diagnoses of MPE in developed countries are metastatic breast or lung carcinomas, lymphoma and mesothelioma. Chemical pleurodesis (administering talc slurry or tetracycline via a chest tube) is as effective as surgical pleurodesis for MPE, and avoids the need for anaesthesia and operating theatre time.[59] In cases where pleurodesis fails (approx 40%),[61,62] repeated thoracenteses, pleuro-peritoneal shunting or indwelling small-bore catheter drainage can be considered. If the patient does not have symptomatic improvement from removal of the pleural effusion (eg if the lung is trapped), pleurodesis is not indicated.

For patients with poor life expectancy or poor performance status, recurrent thoracenteses (whenever symptomatic) may be more appropriate than pleurodesis. In the terminal stage, the use of oxygen and narcotic agents to control the symptom of dyspnoea are preferred over invasive interventions.[59]

If mesothelioma is diagnosed, it is recommended that palliative radiotherapy (21Gy in three doses over 3 days) be administered to the sites of pleural puncture to prevent subsequent needle tract metastases.[57] A randomised trial has demonstrated that this can reduce the risk of tumour metastases virtually to zero.[12]

Tuberculous (TB) Effusions

The incidence of TB pleuritis varies significantly worldwide, and even among regions in the U.K. In endemic countries, it is as common as MPE.[66-68] TB pleural effusions are often difficult to diagnose; the number of organisms present in the pleural space is often low and pleural fluid analysis and pleural tissue culture are often negative. In >50% of patients, TB pleuritis represents a primary infection,[69] with no disease activity elsewhere.

TB pleural fluid is usually a lymphocytic exudate[70, 71] with low glucose and pH. Pleural biopsy is useful (sensitivity >80%).[72] A high level of adenosine deaminase is very suggestive of TB,[71] though false positives can occur in lymphoma, metastatic malignancies or rheumatological diseases.[21]

TB effusions usually resolve spontaneously, with or without anti-mycobacterial therapy. However, if left untreated, about 60% of patients will develop TB in other organ systems within the following few years.[73] The use of systemic steroids or pigtail drainage, both provide symptomatic relief but do not alter treatment outcome, nor the incidence of fibrothorax, wich complicates TB pleuritis.[74, 75, 76]

Pulmonary Embolism

Pulmonary embolism is a recognised cause of pleural effusion. The fluid is usually an exudate, but may be transudative at times. The true incidence of pleural effusion secondary to pulmonary embolism is unknown, but pulmonary emboli should be considered in any undiagnosed case.[77]

Future Directions

Steady and definite progress is being made in pleural disease management. It is important that medical staff recognise the importance of pleural effusion, and early respiratory referral should be encouraged. It is anticipated that image-guidance will be employed more often for pleural procedures, whereas blind pleural biopsy will be used more sparingly. The availability of medical thoracoscopy is growing and its use will be more widely accepted and applied in coming years.

Management of Pleural Effusions in Acute Medical Settings: a practical guide

References

1. Marel M, Zrustova M, Stasny B, Light RW. The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia. *Chest* 1993; **104:** 1486-9.
2. Maskell NA, Butland RJA. The investigation of an undiagnosed pleural effusion in adults. *Thorax* 2003; **58**(suppl 2): ii8-17.
3. Antunes G, Neville E, Duffy J, Ali N. Management of malignant pleural effusions. *Thorax* 2003; **58**(suppl 2): ii 29-38
4. Davies CWH, Gleeson FV, Davies RJO. The British Thoracic Society guidelines on the management of pleural infection. *Thorax* 2003; 58(suppl2): ii 18-28
5. Sahn SA. Approach to the patient with pleural diseases. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London, U.K.: Arnold Press, 2003; 183-190.
6. Davies CL, Gleeson FV. Diagnostic Radiology. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London: Arnold Press, 2003; 210-237.
7. Eibenberger KL, Dock WI, Ammann ME, Dorffner R, Hormann MF, Grabenwoger F. Quantification of pleural effusions: sonography versus radiography. *Radiology* 1994; **191:** 681-684.
8. Jones PW, Moyers JP, Rogers JT, Rodriguez RM, Lee YCG, Light RW. Ultrasound-guided thoracentesis. Is it a safer method? *Chest* 2003; **123:** 418-423.
9. Diacon AH, Brutsche MH, Soler M. Accuracy of pleural puncture sites: a prospective comparison of clinical examination with ultrasound. *Chest* 2003; **123:** 436-441.
10. Light RW. *Pleural Diseases*. In: Light RW, ed. Baltimore: Lippincott, Williams & Wilkins, 2001.
11. Peto J, Hodgson JT, Matthews FE, Jones JR. Continuing increase in mesothelioma mortality in Britain. *Lancet* 1995; **345:** 535-9.
12. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of radiotherapy. *Chest* 1995; **108:** 754-8.
13. Colt H. Drainage and biopsy techniques. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London: Arnold Press, 2003; 481-497.
14. Lan RS, Lo SK, Chuang ML, Yang CT, Tsao TC, Lee CH. Elastance of the pleural space: a predictor for the outcome of pleurodesis in patients with malignant pleural effusion. *Ann Intern Med* 1997; **126:** 768-74.
15. Maskell NA, Gleeson FV, Davies RJO. *Lancet* 2003; **361:** 1326-30
16. Mungall IP, Cowen PN, Cooke NT, Roach TC, Cooke NJ. Multiple pleural biopsy with the Abrams needle. *Thorax* 1980; **35:** 600-602.
17. Tomlinson JR. Invasive procedures in the diagnosis of pleural disease. *Semin Resp Med* 1987; **9:** 30-36.
18. Chretien J, Bignon J, Hirsch A. *The Pleura in Health and Disease*. New York: Marcel Dekker, 1985.
19. McAleer JJ, Murphy GJ, Quinn RJ. Needle biopsy of the pleura in the diagnosis of pleural effusion. *Ulster Med J* 1987; **56:** 54-57.
20. Perez-Rodriguez E, Jimenez Castro D. The use of adenosine deaminase and adenosine deaminase isoenzymes in the diagnosis of tuberculous pleuritis. *Curr Opin Pulm* Med 2000; **6:** 259-66.
21. Lee YCG, Rogers JT, Rodriguez RM, Miller KD, Light RW. Adenosine deaminase levels in nontuberculous lymphocytic pleural effusions. *Chest* 2001; **120:** 356-61.
22. Nagesh BS, Sehgal S, Jindal SK, Arora SK. Evaluation of polymerase chain reaction for detection of Mycobacterium tuberculosis in pleural fluid. *Chest* 2001; **119:** 1737-41.
23. Villegas MV, Labrada LA, Saravia NG. Evaluation of polymerase chain reaction, adenosine deaminase, and interferon-gamma in pleural fluid for the differential diagnosis of pleural tuberculosis. *Chest* 2000; **118:** 1355-64.
24. Light RW, Macgregor MI, Luchsinger PC, Ball WC, Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Medicine* 1972; **77:** 507-13.
25. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. *Chest* 1997; **111:** 970-80.
26. Heffner JE, Sahn SA, Brown LK. Multilevel likelihood ratios for identifying exudative pleural effusions. *Chest* 2002; **121:** 1916-20.
27. Light RW. Useful tests on the pleural fluid in the management of patients with pleural effusions. *Curr Opin Pulm Med* 1999; **5:** 245-9.
28. Sahn SA, Heffner JE. Pleural fluid analysis. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London, U.K.: Arnold Press, 2003; 191-209.
29. Adelman M, Albelda SM, Gottlieb J, Haponik EF. Diagnostic utility of pleural fluid eosinophilia. *Am J Med* 1984; **77:** 915-20.
30. Light RW, Rogers JT, Cheng D, Rodriguez RM, Cardiovascular Surgery Associates. Large pleural effusions occurring after coronary artery bypass grafting. *Ann Intern Med* 1999; **130:** 891-6.
31. Robinson BWS, Musk AW. Benign asbestos pleural effusion: diagnosis and course. *Thorax* 1981; **36:** 896-900.
32. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions. *Chest* 2000; **117:** 79-86.
33. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure. *Chest* 2000; **117:** 87-95.
34. Ferrer A, Osset J, Alegre J, *et al.* Prospective clinical and microbiological study of pleural effusions. *Eur J Clin Microbiol Infect Dis* 1999; **18:** 237-41.
35. Sallach SM, Sallach JA, Vasquez E, Schultz L, Kvale P. Volume of pleural fluid required for diagnosis of pleural malignancy. *Chest* 2002; **122:** 1913-7.
36. Branca P, Rodriguez RM, Rogers JT, Ayo DS, Moyers JP, Light RW. Routine measurement of pleural fluid amylase is not indicated. *Arch Intern Med* 2001; **161:** 228-32.
37. Villena V, Perez V, Pozo F, *et al.* Amylase levels in pleural effusions: a consecutive unselected series of 841 patients. *Chest* 2002; **121:** 470-4.
38. Hillerdal G. Effusions from lymphatic disruptions. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London: Arnold Press, 2003: 362-369.
39. Lee YCG, Lane KB. Cytokines in Pleural Diseases. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London: Arnold Press, 2003; 63-89.
40. Logue RB, Rogers JVJ, Gay BBJ. Subtle roentgenographic signs of left heart failure. *Am Heart J* 1963; **65:** 464-473.
41. Weiss JM, Spodick DH. Laterality of pleural effusions in congestive heart failure. *Am J Cardiol* 1984; **53:** 951-953.
42. Kataoka H. Pericardial and pleural effusions in decompensated chronic heart failure. *Am Heart J* 2000; **139:** 918-923.
43. Kinasewitz GT, Eid AA. Effusion from cardiac diseases. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London, U.K.: Arnold Press, 2003; 282-296.
44. Broaddus VC, Wiener-Kronish JP, Staub NC. Clearance of lung edema into the pleural space of volume-loaded anesthetized sheep. *J Appl Physiol* 1990; **68:** 2623-30.
45. Glazer M, Berkman N, Lafair JS, Kramer MR. Successful talc slurry pleurodesis in patients with nonmalignant pleural effusion: Report of 16 cases and review of the literature. *Chest* 2000; **117:** 1404-1409.
46. Sahn SA. Management of complicated parapneumonic effusions. *Am Rev Respir Dis* 1993; **148:** 813-817.
47. Maskell NA, Davies RJO. Effusions from parapneumonic infection and empyema. In: Light RW, Lee YCG, eds. *Textbook of Pleural Diseases*. London, U.K.: Arnold Press, 2003; 310-328.
48. Sahn SA, Light RW. The sun should never set on a parapneumonic effusion. *Chest* 1989; **95:** 945-7.

49. Heffner JE, McDonald J, Barbieri C, Klein J. Management of parapneumonic effusions. An analysis of physician practice patterns. *Arch Surg* 1995; **130:** 433-8.
50. Light RW. What is the best way to manage parapneumonic effusions. International Pleural Newsletter 2003,1: 1-2; http://www.chestnet.org/networks.
51. Bouros D, Schiza S, Patsourakis G, Chalkiadakis G, Panagou P, Siafakas NM. Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions. *Am J Respir Crit Care Med* 1997; **155:** 291-5.
52. Davies RJO, Traill ZC, Gleeson FV. Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. *Thorax* 1997; **52:** 416-421.
53. Bouros D, Schiza S, Tzanakis N, Chalkiadakis G, Drositis J, Siafakas NM. Intrapleural urokinase versus normal saline in the treatment of complicated parapneumonic effusions and empyema. *Am J Respir Crit Care Med* 1999; **159:** 37-42.
54. Lim TK, Chin NK. Empirical treatment with fibrinolysis and early surgery reduces the duration of hospitalization in pleural sepsis. *Eur Respir J* 1999; **13:** 514-518.
55. Sahn SA. Malignancy metastatic to the pleura. *Clin Chest Med* 1998; **19:** 351-61.
56. Peto J, Decarli A, La Vecchia C, Levi F, Negri E. The European mesothelioma epidemic. *Br J Cancer* 1999; **79:** 666-672.
57. Lee YCG, De Klerk NH, Henderson DW, Musk AW. Malignant mesothelioma. In: Hendrick DJ, Burge PS, Beckett WS, Churg A, eds. *Occupational Disorder of the Lung.* Recognition, Management and Prevention. London, U.K.: W B Saunders & Co., 2002; 359-379.
58. Grove CS, Lee YCG. Vascular endothelial growth factor: the key mediator in pleural effusion formation. *Curr Opin Pulm Med* 2002; **8:** 294-301.
59. Lee YCG, Rodriguez RM, Lane KB, Light RW. Pleurodesis for recurrent pleural effusions in the new millenium. *Recent Advances and Research Updates* 2001; **2:** 81-89.
60. Adams RF, Gleeson FV. Percutaneous image-guided cutting-needle biopsy of the pleura in the presence of a suspected malignant effusion. *Radiology* 2001; **219:** 510-4.
61. Lee YCG, Baumann MH, Maskell NA, *et al.* Pleuiodesis practice for malignant pleural effusions in five English -speaking countries: survey of pulmonologists. *Chest* 2003; **124:** 2229-38.
62. Lee YCG, Baumann MH, Waterer GW, *et al.* Physicians' evaluation of common pleurodesing agents: an international survey. *Am J Respir Crit Care Med* 2002; **165:** A609.
63. Sahn SA. Talc should be used for pleurodesis. *Am J Respir Crite Care Med* 2000; **162:** 2023-2024.
64. Light RW. Talc should not be used for pleurodesis. *Am J Respir Crit Care Med* 2000; **162:** 2024-2026.
65. Light RW. Talc for pleurodesis? *Chest* 2002; **122:** 1506-8.
66. Valdes L, Alvarez D, Valle JM, Pose A, San Jose E. The etiology of pleural effusions in an area with high incidence of tuberculosis. *Chest* 1996; **109:** 158-62.
67. Liam CK, Lim KH, Wong CM. Causes of pleural exudates in a region with a high incidence of tuberculosis. *Respirology* 2000; **5:** 33-8.
68. Kalaajieh WK. Etiology of exudative pleural effusions in adults in North Lebanon. *Can Respir J* 2001; **8:** 93-7.
69. Seibert AF, Haynes JJ, Middleton R, Bass JBJ. Tuberculous pleural effusion. Twenty-year experience. *Chest* 1991; **99:** 883-6.
70. Bothamley GH. Tuberculous pleurisy and adenosine deaminase. *Thorax* 1995; **50:** 593-594.
71. Valdes L, Alvarez D, San Jose E, *et al.* Tuberculous pleurisy: a study of 254 patients. *Arch Intern Med* 1998; **158:** 2017-21.
72. Kirsch CM, Kroe DM, Azzi RL, Jensen WA, Kagawa FT, Wehner JH. The optimal number of pleural biopsy specimens for a diagnosis of tuberculous pleurisy. *Chest* 1997; **112:** 702-6.
73. Roper WH, Waring JJ. Primary serofibrinous pleural effusions in military personnel. *Am Rev Respir Dis* 1955; **71:** 616-634.
74. Matchaba PT, Volmink J. Steroids for treating tuberculous pleurisy. *Cochrane Database Syst Rev* 2000; **2:** CD001876.
75. Wyser C, Walzl G, Smedema JP, Swart F, van Schalkwyk EM, van de Wal BW. Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomized study. *Chest* 1996; **110:** 333-8.
76. Lai YF, Chao TY, Wang YH, Lin AS. Pigtail drainage in the treatment of tuberculous pleural effusions: a randomised study. *Thorax* 2003; **58:** 149-51.
77. Light RW. Pleural effusion due to pulmonary emboli. *Curr Opin Pulm Med* 2001; **7:** 198-201.