BTS guidelines for the investigation of a unilateral pleural effusion in adults

N A Maskell, R J A Butland, on behalf of the British Thoracic Society Pleural Disease Group, a subgroup of the British Thoracic Society Standards of Care Committee

Thorax 2003;**58**(Suppl II):ii8–ii17

1 INTRODUCTION

Pleural effusions, the result of the accumulation of fluid in the pleural space, are a common medical problem. They can be caused by several mechanisms including increased permeability of the pleural membrane, increased pulmonary capillary pressure, decreased negative intrapleural pressure, decreased oncotic pressure, and obstructed lymphatic flow. The pathophysiology of pleural effusions is discussed in more detail in the guideline on malignant effusions (page ii29).

Pleural effusions indicate the presence of disease which may be pulmonary, pleural, or extrapulmonary. As the differential diagnosis is wide, a systematic approach to investigation is necessary. The aim is to establish a diagnosis swiftly while minimising unnecessary invasive investigation. This is particularly important as the differential diagnosis includes malignant mesothelioma in which 40% of needle incisions for investigation are invaded by tumour.[1] A minimum number of interventions is therefore appropriate.

A diagnostic algorithm for the investigation of a pleural effusion is shown in fig 1.

2 CLINICAL ASSESSMENT AND HISTORY

- **Aspiration should not be performed for bilateral effusions in a clinical setting strongly suggestive of a pleural transudate, unless there are atypical features or they fail to respond to therapy. [C]**
- **An accurate drug history should be taken during clinical assessment. [C]**

The initial step in assessing a pleural effusion is to ascertain whether it is a transudate or exudate. Initially this is through the history and physical examination. The biochemical analysis of pleural fluid is considered later (section 5).

Clinical assessment alone is often capable of identifying transudative effusions. In a series of 33 cases, all 17 transudates were correctly predicted by clinical assessment, blind of the results of pleural fluid analysis.[2] Therefore, in an appropriate clinical setting such as left ventricular failure with a confirmatory chest radiograph, these effusions do not need to be sampled unless there are atypical features or they fail to respond to treatment.

Approximately 75% of patients with pulmonary embolism and pleural effusion have a history of pleuritic pain. These effusions tend to occupy less than a third of the hemithorax and the dyspnoea is often out of proportion to its size. As tests on the pleural fluid are unhelpful in diagnosing pulmonary embolism, a high index of suspicion is required to avoid missing the diagnosis.[3]

The patient's drug history is also important. Although uncommon, a number of medications have been reported to cause exudative pleural effusions. These are shown in box 1, together with their frequencies. Useful resources for more detailed information include the *British National Formulary* and the website pneumotox.com.

3 CAUSES OF A PLEURAL EFFUSION

Pleural effusions are classified into transudates and exudates. A transudative pleural effusion occurs when the balance of hydrostatic forces influencing the formation and absorption of pleural fluid is altered to favour pleural fluid accumulation. The permeability of the capillaries to proteins is normal.[4] In contrast, an exudative pleural effusion develops when the pleural surface and/or the local capillary permeability are altered.[5] There are a multitude of causes of transudates and exudates and these are shown in boxes 2 and 3, together with a guide to their frequency.

4 PLEURAL ASPIRATION

- **A diagnostic pleural fluid sample should be gathered with a fine bore (21G) needle and a 50 ml syringe. The sample should be placed in both sterile vials and blood culture bottles and analysed for protein, lactate dehydrogenase (LDH, to clarify borderline protein values), pH, Gram stain, AAFB stain, cytology, and microbiological culture. [C]**

This is the primary means of evaluating pleural fluid and its findings are used to guide further investigation. Diagnostic taps are often performed in the clinic or by the bedside, although small

Box 1 Drugs known to cause pleural effusions

Over 100 reported cases globally*

- Amiodarone
- Nitrofurantoin
- Phenytoin
- Methotrexate

20–100 reported cases globally*

- Carbamazepine
- Procainamide
- Propylthiouracil
- Penicillamine
- GCSF
- Cyclophosphamide
- Bromocriptine

*pneumotox.com (2001)

See end of article for authors' affiliations

Correspondence to: Dr N A Maskell, Oxford Centre for Respiratory Medicine, Churchill Hospital Site, Oxford Radcliffe Hospital, Headington, Oxford OX3 7LJ, UK; nickmaskell@doctors.org.uk

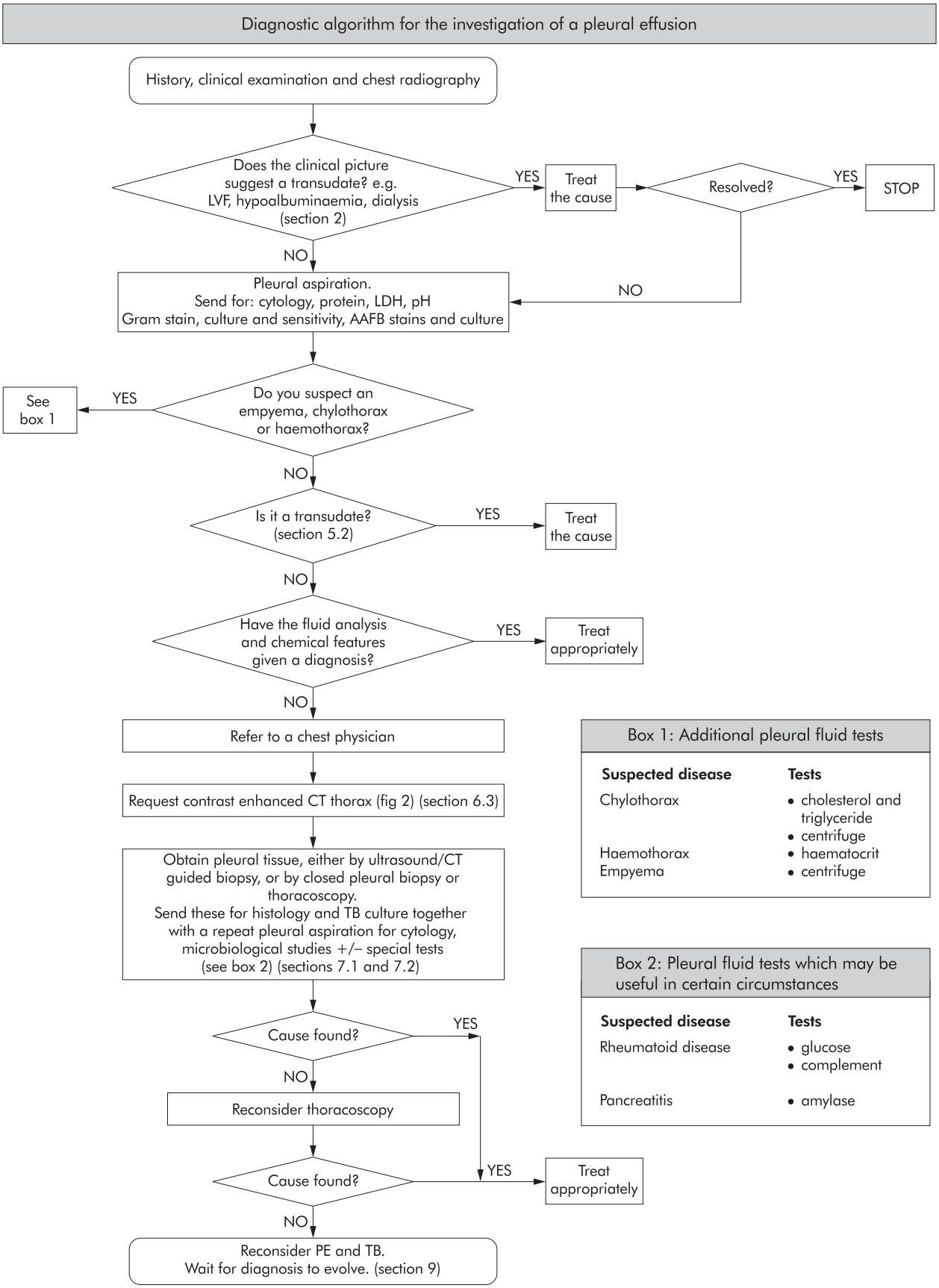

Figure 1 Flow diagram of the investigation pathway for a unilateral pleural effusion of unknown aetiology.

Box 2 Causes of transudative pleural effusions

Very common causes
- Left ventricular failure
- Liver cirrhosis
- Hypoalbuminaemia
- Peritoneal dialysis

Less common causes
- Hypothyroidism
- Nephrotic syndrome
- Mitral stenosis
- Pulmonary embolism

Rare causes
- Constrictive pericarditis
- Urinothorax
- Superior vena cava obstruction
- Ovarian hyperstimulation
- Meigs' syndrome

Box 3 Causes of exudative pleural effusions

Common causes
- Malignancy
- Parapneumonic effusions

Less common causes
- Pulmonary infarction
- Rheumatoid arthritis
- Autoimmune diseases
- Benign asbestos effusion
- Pancreatitis
- Post-myocardial infarction syndrome

Rare causes
- Yellow nail syndrome
- Drugs (see box 1)
- Fungal infections

effusions often require radiological guidance. A green needle (21G) and 50 ml syringe are adequate for diagnostic pleural taps. The 50 ml sample should be split into three sterile pots to be sent directly for microbiological, biochemical, and cytological analysis.

Microscopic examination of Gram stained pleural fluid sediment is necessary for all fluids and particularly when a parapneumonic effusion is suspected. If some of the microbiological specimen is sent in blood culture bottles the yield is greater, especially for anaerobic organisms.[6]

20 ml of pleural fluid is adequate for cytological examination and the fresher the sample when it arrives at the laboratory the better. If part of the sample has clotted, the cytologist must fix and section this and treat it as a histological section as it will increase the yield. Sending the cytology sample in a citrate bottle will prevent clots and is preferred by some cytologists. If delay is anticipated, the specimen can be stored at 4°C for up to 4 days.[7]

5 PLEURAL FLUID ANALYSIS

5.1 Typical characteristics of the pleural fluid

- **The appearance of the pleural fluid and any odour should be noted. [C]**
- **A pleural fluid haematocrit is helpful in the diagnosis of haemothorax.**

After performing pleural aspiration, the appearance and odour of the pleural fluid should be noted. The unpleasant aroma of anaerobic infection may guide antibiotic choice. The appearance can be divided into serous, blood tinged, frankly bloody, or purulent. If the pleural fluid is turbid or milky it should be centrifuged. If the supernatant is clear, the turbid fluid was due to cell debris and empyema is likely. If it is still turbid, this is because of a high lipid content and a chylothorax or pseudochylothorax are likely.[8] Table 1 lists the characteristics of the pleural fluid in certain pleural diseases.

If the pleural fluid appears bloody, a haematocrit can be obtained if there is doubt as to whether it is a haemothorax. If the haematocrit of the pleural fluid is more than half of the patient's peripheral blood haematocrit, the patient has a haemothorax. If the haematocrit on the pleural fluid is less than 1%, the blood in the pleural fluid is not significant.[9] Grossly bloody pleural fluid is usually due to malignancy, pulmonary embolus with infarction, trauma, benign asbestos pleural effusions, or post-cardiac injury syndrome (PCIS).[9]

Box 4 Key facts when investigating undiagnosed pleural effusions

- If the pleural fluid protein is between 25 and 35 g/l, then Light's criteria are advised to differentiate accurately exudates from transudates.
- Pleural fluid pH should be performed in all non-purulent effusions if infection is suspected.
- When sending a pleural fluid specimen for microbiological examination, it should be sent in both a sterile tube (for Gram stain, AAFB and TB culture) and in blood culture bottles to increase the diagnostic yield.
- Only 60% of malignant effusions can be diagnosed by cytological examination.
- A contrast enhanced CT scan of the thorax is best performed with the fluid present. This will enable better visualisation of pleura and can identify the best site for pleural biopsy if cytological examination is unhelpful.

Table 1 Appearance of pleural fluid

Fluid	Suspected disease
Putrid odour	Anaerobic empyema
Food particles	Oesophageal rupture
Bile stained	Cholothorax (biliary fistula)
Milky	Chylothorax/pseudochylothorax
"Anchovy sauce" like fluid	Ruptured amoebic abscess

5.2 Differentiating between a pleural fluid exudate and transudate

- **The pleural protein should be measured to differentiate between a transudative and exudative pleural effusion. This will usually suffice if the patient's serum protein is normal and pleural protein is less than 25 g/l or more than 35 g/l. If not, Light's criteria (see box 5) should be used. [B]**

The classical way of separating a transudate from an exudate is by pleural fluid protein, with exudates having a protein level of >30 g/l and transudates a protein level of <30 g/l. Care should be taken in interpreting this result if the serum total protein is abnormal. Unfortunately, the protein level often lies very close to the 30 g/l cut off point, making clear differentiation difficult. In these cases, measurement of serum and pleural fluid lactate dehydrogenase (LDH) and total protein levels will allow the use of Light's criteria to distinguish between these two more accurately (box 5).[10]

A considerable number of other biochemical markers have been compared with Light's criteria. These include measuring pleural fluid cholesterol, albumin gradient, and serum/pleural fluid bilirubin ratio.[11–15] The accuracy of these different indices

Box 5 Light's criteria

The pleural fluid is an exudate if one or more of the following criteria are met:
- Pleural fluid protein divided by serum protein >0.5
- Pleural fluid LDH divided by serum LDH >0.6
- Pleural fluid LDH more than two-thirds the upper limits of normal serum LDH

in differentiating exudates and transudates has been examined in a meta-analysis of 1448 patients from eight studies.[15] Light's criteria performed best with excellent discriminative properties. Further analysis suggests a cut off value of LDH levels in pleural fluid of >0.66, the upper limits of the laboratory normal might be a better discriminator ("modified Light's criteria").[16]

In summary, Light's criteria appear to be the most accurate way of differentiating between transudates and exudates. The weakness of these criteria is that they occasionally identify an effusion in a patient with left ventricular failure on diuretics as an exudate. In this circumstance, clinical judgement should be used.

5.3 Differential cell counts on the pleural fluid

- **Pleural lymphocytosis is common in malignancy and tuberculosis.**
- **Eosinophilic pleural effusions are not always benign.**

When polymorphonuclear cells predominate, the patient has an acute process affecting the pleural surfaces. If there is concomitant parenchymal shadowing, the most likely diagnoses are parapneumonic effusion and pulmonary embolism with infarction. If there is no parenchymal shadowing, more frequent diagnoses are pulmonary embolism, viral infection, acute tuberculosis, or benign asbestos pleural effusion.[9 17]

An eosinophilic pleural effusion is defined as the presence of 10% or more eosinophils in the pleural fluid. The presence of pleural fluid eosinophilia is of little use in the differential diagnosis of pleural effusions.[9] Benign aetiologies include parapneumonic effusions, tuberculosis, drug induced pleurisy, benign asbestos pleural effusions, Churg-Strauss syndrome, pulmonary infarction, and parasitic disease.[18–20] It is often the result of air or blood in the pleural cavity.[19] However, malignancy is also a common cause; 11 of a series of 45 eosinophilic effusions were due to cancer.[20]

If the pleural fluid differential cell count shows a predominant lymphocytosis, the most likely diagnoses are tuberculosis and malignancy. Although high lymphocyte counts in pleural fluid raise the possibility of tuberculous pleurisy,[9] as many as 10% of tuberculous pleural effusions are predominantly neutrophilic.[21] Lymphoma, sarcoidosis, rheumatoid disease, and chylothorax can cause a lymphocytic pleural effusion.[22]

Coronary artery bypass grafting (CABG) often causes pleural effusions which can usually be treated conservatively. Large symptomatic effusions can occur in up to 1% of patients in the postoperative period. These are predominantly left sided and the differential cell count can help to clarify the situation. Bloody effusions are usually eosinophilic, occur early, and are related to bleeding into the pleural cavity from the time of surgery. Non-bloody effusions tend to have small lymphocytes as their predominant cell type, occur later, and are generally more difficult to treat.[23]

5.4 pH

- **pH should be performed in all non-purulent effusions. [B]**
- **In an infected effusion a pH of <7.2 indicates the need for tube drainage. [B]**

A pleural fluid pH of <7.2 with a normal blood pH is found in the same diagnoses as a low pleural fluid glucose.[24] A pH of <7.2 represents a substantial accumulation of hydrogen ions, as normal pleural pH is about 7.6 because of bicarbonate accumulation in the pleural cavity. The main clinical use for the measurement of pleural pH is the identification of pleural infection.[25 26] This is covered in detail in the guideline on pleural infection (page ii18). Other diseases causing an exudative pleural effusion with a low pH are collagen vascular diseases (particularly rheumatoid arthritis), oesophageal rupture, and malignancy.[24]

A prospective study of the value of pH in malignant pleural effusions by Rodriguez and Lopez[27] in 77 patients undergoing thoracoscopy showed that a pH of <7.3 was associated with more extensive malignancy, a 90% chance of positive cytology, and a 50% chance of failed pleurodesis. Sahn and Good showed that a reduced pH (<7.3) predicted poor survival in malignant pleural disease (pH >7.3, median survival 9.8 months; pH <7.3, survival 2.1 months).[28]

5.5 Glucose

A pleural glucose level of less than 3.3 mmol/l is found in exudative pleural effusions secondary to empyema, rheumatoid disease, lupus, tuberculosis, malignancy, or oesophageal rupture.[29] The lowest glucose concentrations are found in rheumatoid effusions and empyema.[29–32] In pleural infection, pH discriminates better than glucose.[26 33] Rheumatoid arthritis is unlikely to be the cause of an effusion if the glucose level in the fluid is above 1.6 mmol/l (see section 8.6.1).[30]

5.6 Amylase

- **Amylase measurement should be requested if acute pancreatitis or rupture of the oesophagus is possible. [C]**
- **Iso-enzyme analysis is useful in differentiating high amylase levels secondary to malignancy or ruptured oesophagus from those raised in association with abdominal pathology.**

Pleural fluid amylase levels can be useful in the evaluation of an exudative effusion. Pleural fluid amylase levels are elevated if they are higher than the upper limits of normal for serum or the pleural fluid/serum ratio is >1.0.[31] This suggests acute pancreatitis, pancreatic pseudocyst, rupture of the oesophagus, ruptured ectopic pregnancy, or pleural malignancy (especially adenocarcinoma).[9] Approximately 10% of malignant effusions have raised pleural amylase levels.[34]

Iso-enzyme analysis can be useful in suspected cases of oesophageal rupture as this will show the amylase is of salivary origin.[35] If the salivary amylase is raised and oesophageal rupture is not suspected, malignancy is most likely. Pleural effusions associated with pancreatic disease usually contain pancreatic amylase.[36]

In a prospective study of 176 patients, 10 had an amylase rich effusion. Of these, four had pancreatitis which had not previously been suspected. The rest were due to non-pancreatic diseases of which lung cancer was predominant.[37] The incidence of pleural effusion with acute pancreatitis exceeds 50%. Patients with acute pancreatitis and a pleural effusion tend to have more severe disease and a higher likelihood of subsequently developing a pseudocyst than those without effusions.[38]

5.7 Cytology

- **Malignant effusions can be diagnosed by pleural fluid cytology alone in only 60% of cases.**
- **If the first pleural cytology specimen is negative, this should be repeated a second time. [B]**
- **Both cell blocks and fluid smears should be prepared for examination and, if the fluid has clotted, it needs to be fixed and sectioned as a histological section. [B]**

Table 2 Sensitivity of pleural fluid cytology in malignant pleural effusion

Reference	No of patients	No caused by malignancy	% diagnosed by cytology
Salyer *et al*[40]	271	95	72.6
Prakash *et al*[42]	414	162	57.6
Nance *et al*[41]	385	109	71.0
Hirsch[39]	300	117	53.8
Total	1370	371	61.6

If malignancy is suspected, cytological examination of the pleural fluid is a quick and minimally invasive way to obtain a diagnosis. The results of the major series reporting the sensitivity of pleural cytology are shown in table 2.[39–42] These sensitivities vary from 40% to 87%, with a mean of about 60%. Of 55 cases where malignancy was diagnosed on the basis of cytological examination, Garcia *et al* found 65% were established from the first specimen, a further 27% from the second, and only 5% from the third.[43]

A retrospective review of 414 patients between 1973 and 1982 compared the diagnostic efficacy of cytology alone and in combination with pleural biopsy.[42] The final causes of the effusion were malignancy in 281 patients (68%). The presence of pleural malignancy was established by cytology in 162 patients (58%) and, with the addition of a blind pleural biopsy, a further 20 patients (7%) were classified as having malignancy. The yield depends on the skill and interest of the cytologist and on tumour type, with a higher diagnostic rate for adenocarcinoma than for mesothelioma, squamous cell carcinoma, lymphoma and sarcoma. The yield increases if both cell blocks and smears are prepared.[44]

Immunocytochemistry, as an adjunct to cell morphology, is becoming increasingly helpful in distinguishing benign from malignant mesothelial cells and mesothelioma from adenocarcinoma.[45 46] Epithelial membrane antigen (EMA) is widely used to confirm a cytological diagnosis of epithelial malignancy.[46 47] When malignant cells are identified, the glandular markers for CEA, B72.3 and Leu-M1 together with calretinin and cytokeratin 5/6 will often help to distinguish adenocarcinoma from mesothelioma.[46–48]

6 DIAGNOSTIC IMAGING

6.1 Plain radiography

- **PA and lateral chest radiographs should be performed in the assessment of suspected pleural effusion. [C]**

The plain chest radiographic features of pleural effusion are usually characteristic. The PA chest radiograph is abnormal in the presence of about 200 ml pleural fluid. However, only 50 ml of pleural fluid can produce detectable posterior costophrenic angle blunting on a lateral chest radiograph.[49] Lateral decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating between pleural thickening and free fluid.[50]

In the intensive care setting, patients are often imaged supine where free pleural fluid will layer out posteriorly. Pleural fluid is often represented as a hazy opacity of one hemithorax with preserved vascular shadows on the supine radiograph. Other signs include the loss of the sharp silhouette of the ipsilateral hemidiaphragm and thickening of the minor fissure. The supine chest radiograph will often underestimate the volume of pleural fluid.[51]

Subpulmonic effusions occur when pleural fluid accumulates in a subpulmonic location. They are often transudates and can be difficult to diagnose on the PA radiograph and may require a lateral decubitus view or ultrasound. The PA radiograph will often show a lateral peaking of an apparently raised hemidiaphragm which has a steep lateral slope with gradual medial slope. The lateral radiograph may have a flat appearance of the posterior aspect of the hemidiaphragm with a steep downward slope at the major fissure.[52]

6.2 Ultrasound findings

- **Ultrasound guided pleural aspiration should be used as a safe and accurate method of obtaining fluid if the effusion is small or loculated. [B]**
- **Fibrinous septations are better visualised on ultrasound than on CT scans.**

Ultrasound is more accurate than plain chest radiography for estimating pleural fluid volume and aids thoracentesis.[53 54] After unsuccessful thoracentesis or in a loculated pleural effusion, ultrasound guided aspiration yields fluid in 97% of cases.[50] In a series of 320 patients, Yang *et al*[55] found that pleural effusions with complex septated, complex non-septated, or homogeneously echogenic patterns are always exudates, whereas hypoechoic effusions can be either transudates or exudates. Ultrasound is also useful in demonstrating fibrinous loculation and readily differentiates between pleural fluid and pleural thickening.[56 57] Ultrasound also has the added advantage of often being portable, allowing imaging at the bedside with the patient sitting or in the recumbent position.[58 59]

6.3 CT findings

- **CT scans for pleural effusion should be performed with contrast enhancement. [C]**
- **In cases of difficult drainage, CT scanning should be used to delineate the size and position of loculated effusions. [C]**
- **CT scanning can usually differentiate between benign and malignant pleural thickening.**

There are features of contrast enhanced thoracic CT scanning which can help differentiate between benign and malignant disease (fig 2). In a study of 74 patients, 39 of whom had malignant disease, Leung *et al*[60] showed that malignant disease is favoured by nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening greater than 1 cm, and circumferential pleural thickening. These features have specificities of 94%, 94%, 88%, and 100%, respectively, and sensitivities of 51%, 36%, 56% and 41%. Scott *et al*[61] evaluated these criteria in 42 patients with pleural thickening; 32 of the 33 cases of pleural malignancy were identified correctly on the basis of the presence of one or more of Leung's criteria. When investigating a pleural effusion a contrast enhanced thoracic CT scan should be performed before full drainage of the fluid as pleural abnormalities will be better visualised.[62]

CT scanning has been shown to be superior to plain radiographs in the differentiation of pleural from parenchymal disease. It is particularly helpful in the assessment and management of loculated pleural effusions. Loculated effusions on CT scans tend to have a lenticular shape with smooth margins and relatively homogeneous attenuation.[63]

The role of magnetic resonance (MR) imaging is currently evolving, but generally does not provide better imaging than CT scanning.[59 64 65]

7 INVASIVE INVESTIGATIONS

7.1 Percutaneous pleural biopsy

- **Pleural tissue should always be sent for tuberculosis culture whenever a biopsy is performed. [B]**
- **In cases of mesothelioma, the biopsy site should be irradiated to stop biopsy site invasion by tumour. [A]**

Percutaneous pleural biopsies are of greatest value in the diagnosis of granulomatous and malignant disease of the

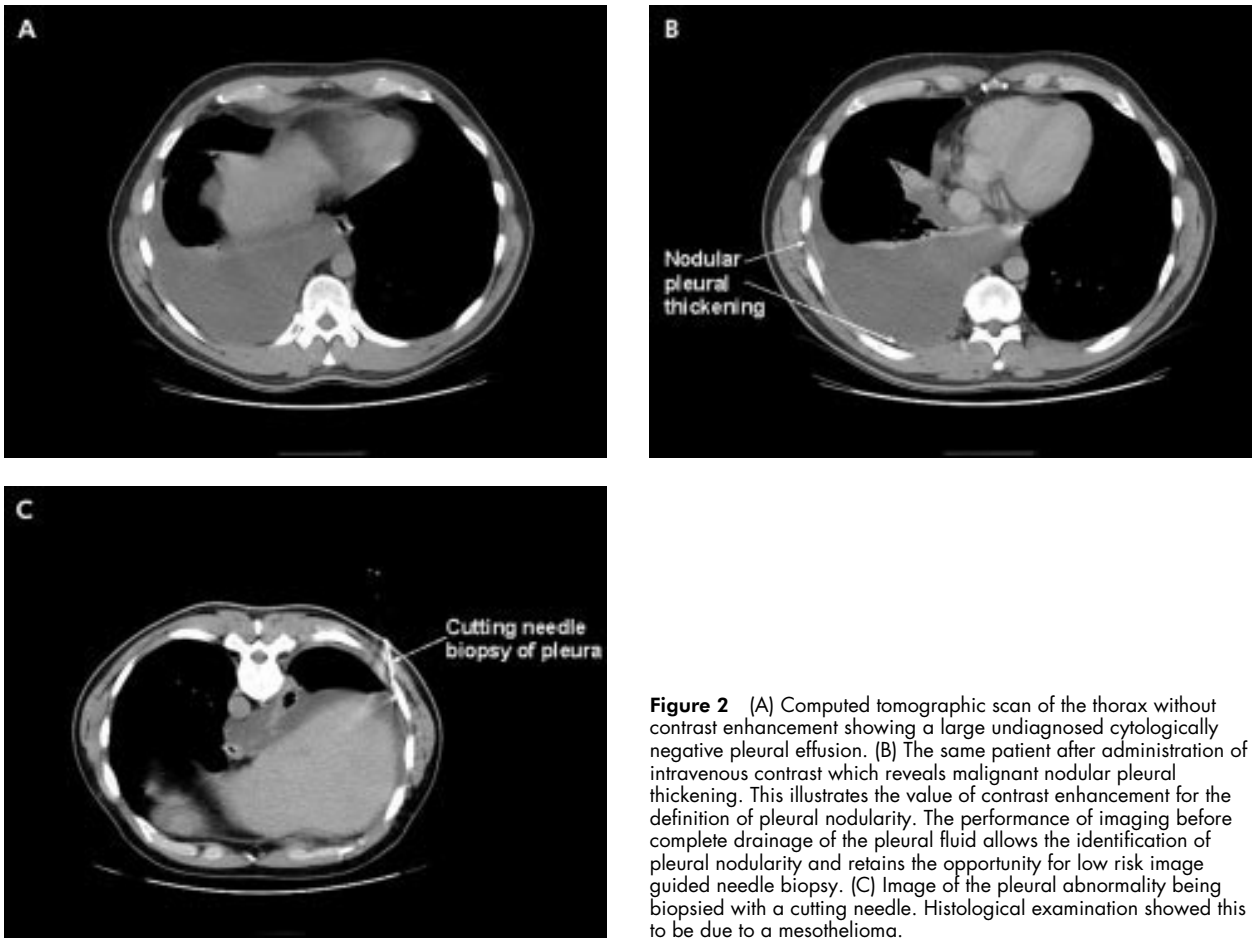

Figure 2 (A) Computed tomographic scan of the thorax without contrast enhancement showing a large undiagnosed cytologically negative pleural effusion. (B) The same patient after administration of intravenous contrast which reveals malignant nodular pleural thickening. This illustrates the value of contrast enhancement for the definition of pleural nodularity. The performance of imaging before complete drainage of the pleural fluid allows the identification of pleural nodularity and retains the opportunity for low risk image guided needle biopsy. (C) Image of the pleural abnormality being biopsied with a cutting needle. Histological examination showed this to be due to a mesothelioma.

pleura. They are performed on patients with undiagnosed exudative effusions, with non-diagnostic cytology, and a clinical suspicion of tuberculosis or malignancy. Occasionally, a blind pleural biopsy may be performed at the same time as the first pleural aspiration if clinical suspicion of tuberculosis is high.

All aspiration and biopsy sites should be marked with Indian ink as the site(s) will need local radiotherapy within 1 month if the final diagnosis is mesothelioma. This is based on a small randomised study showing tumour seeding in the biopsy track in about 40% of the patients who did not receive local radiotherapy.[1] Other clinical trials continue to recruit to clarify this area.

7.1.1 Blind percutaneous pleural biopsies

- **When using an Abrams' needle, at least four biopsy specimens should be taken from one site. [C]**

The Abrams' pleural biopsy needle is most commonly used in the UK with the Cope needle being less prevalent. Morrone *et al*[66] compared these two needles in a small randomised study of 24 patients; the diagnostic yield was similar but samples were larger with an Abrams' needle. The yield compared with pleural fluid cytology alone is increased by only 7–27% for malignancy.[40–42] At least four samples need to be taken to optimise diagnostic accuracy,[67] and these should be taken from one site as dual biopsy sites do not increase positivity.[68] The biopsy specimens should be placed in 10% formaldehyde for histological examination and sterile saline for tuberculosis culture. A review of the pleural biopsy yield from 2893 examinations performed between 1958 and 1985 (published in 14 papers) showed a diagnostic rate of 75% for tuberculosis and 57% for carcinoma.[69] In tuberculous effusions, when fluid AAFB smear, culture, biopsy histology, and culture are performed in concert, the diagnostic yield is 80–90%.[21 70–72]

Complications of Abrams' pleural biopsy include site pain (1–15%), pneumothorax (3–15%), vasovagal reaction (1–5%), haemothorax (<2%), site haematoma (<1%), transient fever (<1%) and, very rarely, death secondary to haemorrhage. If a pneumothorax is caused, only 1% require chest drainage.[69 70 72–75]

7.1.2 Image guided cutting needle pleural biopsies

- **When obtaining biopsies from focal areas of pleural nodularity shown on contrast enhanced CT scans, image guidance should be used. [C]**
- **Image guided cutting needle biopsies have a higher yield for malignancy than standard Abrams' needle pleural biopsy.**

The contrast enhanced thoracic CT scan of a patient with a pleural effusion will often show a focal area of abnormal pleura. An image guided cutting needle biopsy allows that focal area of abnormality to be biopsied. It has a higher yield than that of blind pleural biopsy in the diagnosis of malignancy.[76] This technique is particularly useful in patients who are unsuitable for thoracoscopy.

Pleural malignant deposits tend to predominate close to the midline and diaphragm, which are areas best avoided when performing an Abrams' biopsy. However, it is possible to take biopsy specimens safely from these anatomical regions under radiological imaging.[76–78] In a recent prospective study 33 patients with a pleural effusion and pleural thickening, demonstrated on contract enhanced CT scanning, underwent percutaneous image guided pleural biopsy. Correct histological

diagnosis was made in 21 of 24 patients (sensitivity 88%, specificity 100%) including 13 of 14 patients with mesothelioma (sensitivity 93%).[77] In a larger retrospective review of image guided pleural biopsy in one department by a single radiologist, 18 of 21 mesothelioma cases were correctly identified (sensitivity 86%, specificity 100%).[78] The only published complications to date are local haematoma and minor haemoptysis.

7.2 Thoracoscopy

- **Thoracoscopy should be considered when less invasive tests have failed to give a diagnosis. [B]**

Thoracoscopy is usually used when less invasive techniques (thoracentesis and percutaneous closed pleural biopsy) have not been diagnostic. Harris *et al*[79] described 182 consecutive patients who underwent thoracoscopy over a 5 year period and showed it to have a diagnostic sensitivity of 95% for malignancy. Malignancy was shown by thoracoscopy in 66% of patients who had previously had a non-diagnostic closed pleural biopsy and in 69% of patients who had had two negative pleural cytological specimens. A similar sensitivity for malignant disease was described by Page[80] in 121 patients with undiagnosed effusion.

In addition to obtaining a tissue diagnosis, several litres of fluid can be removed during the procedure and the opportunity is also provided for talc pleurodesis. Thoracoscopy may therefore be therapeutic as well as diagnostic.[81]

Complications of this procedure appear to be few. The most serious, but rare, is severe haemorrhage caused by blood vessel trauma.[81] In a series of 566 examinations by Viskum and Enk[82] the most common side effect was subcutaneous emphysema (6.9%), with cardiac dysrhythmia occurring in 0.35%, one air embolism, and no deaths.

7.3 Bronchoscopy

- **Routine diagnostic bronchoscopy should not be performed for undiagnosed pleural effusion. [C]**
- **Bronchoscopy should be considered if there is haemoptysis or clinical features suggestive of bronchial obstruction. [C]**

Heaton and Roberts[83] reviewed the case records of 32 patients who had bronchoscopy for undiagnosed pleural effusion. In only six did it yield a diagnosis and in four of these the diagnosis was also established by less invasive means. The other two had radiographic abnormalities suggestive of bronchial neoplasm. Upham *et al*[84] studied 245 patients over 2 years and Feinsilver *et al*[85] studied 70. Both also found positive yields of <5% in patients with a pleural effusion, but no haemoptysis or pulmonary abnormality on the chest radiograph. Chang *et al*[86] performed bronchoscopy, thoracentesis, and pleural biopsy on 140 consecutive patients with pleural effusion. In the patient group with an isolated pleural effusion, with no haemoptysis or pulmonary abnormality on the chest radiograph, the yield from bronchoscopy was only 16% whereas pleural investigation yielded a positive diagnosis in 61%. If bronchoscopy is deemed necessary, it should be performed after pleural drainage in order to perform adequate bronchoscopy without extrinsic airway compression by pleural fluid.

Box 6 Causes of chylothorax and pseudochylothorax

Chylothorax

- Neoplasm: lymphoma, metastatic carcinoma
- Trauma: operative, penetrating injuries
- Miscellaneous: tuberculosis, sarcoidosis, lymphangioleiomyomatosis, cirrhosis, obstruction of central veins, amyloidosis

Pseudochylothorax

- Tuberculosis
- Rheumatoid arthritis
- Poorly treated empyema

In summary, bronchoscopy has a limited role in patients with an undiagnosed pleural effusion. It should be reserved for patients whose radiology suggests the presence of a mass, loss of volume or when there is a history of haemoptysis or possible aspiration of a foreign body.

8 SPECIAL TESTS

8.1 Chylothorax and pseudochylothorax

- **If a chylothorax or pseudochylothorax is suspected, pleural fluid should be sent for measurement of triglyceride and cholesterol levels and the laboratory asked to look for the presence of cholesterol crystals and chylomicrons. [C]**

True chylous effusions result from disruption of the thoracic duct or its tributaries. This leads to the presence of chyle in the pleural space. Approximately 50% are due to malignancy (particularly lymphoma), 25% trauma (especially during surgery), and the rest are miscellaneous causes such as tuberculosis, sarcoidosis, and amyloidosis (box 6).[87 88]

Chylothorax must be distinguished from pseudochylothorax or "cholesterol pleurisy" which results from the accumulation of cholesterol crystals in a long standing pleural effusion. In these cases the pleura is usually markedly thickened and fibrotic.[89] In the past, the most common causes of a pseudochylous effusion were tuberculosis and artificial pneumothorax. Chronic rheumatoid pleurisy is now the usual cause.[90 91]

Chylothorax and pseudochylothorax can be discriminated by lipid analysis of the fluid. A true chylothorax will usually have a high triglyceride level, usually >1.24 mmol/l (110 mg/dl), and can usually be excluded if the triglyceride level is <0.56 mmol/l (50 mg/dl). The biochemistry laboratory should be asked to look for the presence of chylomicrons between these values. In a pseudochylothorax the cholesterol level is >5.18 mmol/l (200 mg/dl), chylomicrons are not found, and cholesterol crystals are often seen at microscopy (table 3).[89 92]

Occasionally an empyema can be unusually milky and confused with chylothorax. They can be distinguished by bench centrifugation which leaves a clear supernatant in empyema as the cell debris is separated. The chylous effusion remains milky.

Table 3 Laboratory differentiation of chylothorax and pseudochylothorax

Feature	Pseudochylothorax	Chylothorax
Triglycerides	<0.56 mmol/l (50 mg/dl)	>1.24 mmol/l (110 mg/dl)
Cholesterol	>5.18 mmol/l (200 mg/dl)	<5.18 mmol/l (200 mg/dl)
Cholesterol crystals	Often present	Absent
Chylomicrons	Absent	Present

8.2 Urinothorax

- **If urinothorax is suspected, the pleural fluid creatinine level should be measured and will be higher than the serum creatinine level. [C]**

Urinothorax is a rare complication of an obstructed kidney. The urine is thought to move through the retroperitoneum to enter the pleural space, with the effusion occurring on the same side as the obstructed kidney.[93] The pleural fluid smells like urine and resolves when the obstruction is removed.[94] The diagnosis can be confirmed by demonstrating that the pleural fluid creatinine level is greater than the serum creatinine level. The pleural fluid is a transudate and has a low pH.[95 96]

8.3 Tuberculous pleurisy

- **When pleural biopsies are taken, they should be sent for both histological examination and culture to improve the diagnostic sensitivity for tuberculosis. [B]**

Smears for acid fast bacilli are only positive in 10–20% of tuberculous effusions and are only 25–50% positive on pleural fluid culture.[97 98] The addition of pleural biopsy histology and culture improves the diagnostic rate to about 90%.[21 98]

The adenosine deaminase (ADA) level in pleural fluid tends to be higher with tuberculosis than in other exudates.[100–102] However, ADA levels are also raised in empyema, rheumatoid pleurisy, and malignancy, which makes the test less useful in countries with a low prevalence of tuberculosis. Importantly, ADA levels may not be raised if the patient has HIV and tuberculosis.[103]

8.4 Pleural effusion due to pulmonary embolism

- **There are no specific pleural fluid characteristics to distinguish those caused by pulmonary embolism. This diagnosis should be pursued on clinical grounds.**

Small pleural effusions are present in up to 40% of cases of pulmonary embolism. Of these, 80% are exudates and 20% transudates; 80% are bloodstained.[3 22] A pleural fluid red blood cell count of more than 100 000/mm^3 is suggestive of malignancy, pulmonary infarction, or trauma.[9] Lower counts are unhelpful.[3] Effusions associated with pulmonary embolism have no specific characteristics and the diagnosis should therefore be pursued on clinical grounds with the physician retaining a high index of suspicion for the diagnosis.[22]

8.5 Benign asbestos pleural effusion

Benign asbestos pleural effusions are commonly diagnosed in the first two decades after asbestos exposure. The prevalence is dose related with a shorter latency period than other asbestos related disorders.[104] The effusion is usually small and asymptomatic, often with pleural fluid which is haemorrhagic.[105 106] There is a propensity for the effusion to resolve within 6 months, leaving behind residual diffuse pleural thickening.[105 106] As there are no definitive tests, the diagnosis can only be made with certainty after a prolonged period of follow up.

8.6 Connective tissue diseases

8.6.1 Rheumatoid arthritis associated pleural effusions

- **Suspected cases should have a pleural fluid pH, glucose and complement measured. [C]**
- **Rheumatoid arthritis is unlikely to be the cause of an effusion if the glucose level in the fluid is above 1.6 mmol/l (29 mg/dl).**

Pleural involvement occurs in 5% of patients with rheumatoid arthritis.[107] The majority of patients with rheumatoid pleural effusions are men, even though the disease generally affects more women.[108] Pleural fluid can be serous, turbid, yellow green, milky, or haemorrhagic.[109] Rheumatoid arthritis is unlikely to be the cause of an effusion if the glucose level in the fluid is above 1.6 mmol/l, so this serves as a useful screening test.[30] 80% of rheumatoid pleural effusions have a pleural fluid glucose to serum ratio of <0.5 and a pH <7.30.[109 110] However, in acute rheumatoid pleurisy the glucose level and pH may by normal.[107] Measurement of C4 complement in pleural fluid may be of additional help, with levels below 0.04 g/l in all cases of rheumatoid pleural disease and in only two of 118 controls reported in one study.[108] Rheumatoid factor can be measured on the pleural fluid and often has a titre of >1:320. However, it can be present in effusions of other aetiology and often mirrors the serum value, adding little diagnostically.[108 111]

8.6.2 Systemic lupus erythematosus

- **The pleural fluid ANA level should not be measured as it mirrors serum levels and is therefore unhelpful. [C]**

Up to 50% of patients with systemic lupus erythematosus (SLE) will have pleural disease at some time in the course of their disease.[107] The presence of LE cells in pleural fluid is diagnostic of SLE.[107 112] Khare *et al*[111] measured ANA levels in 82 consecutive pleural effusions. Six of the eight samples collected from patients with SLE were ANA positive with a homogenous staining pattern; the two effusions that were negative for ANA had other reasons for their effusions (pulmonary embolism and left ventricular failure). However, eight (10%) of the effusions where the patients had no clinical evidence of SLE were ANA positive. In five of these eight patients the underlying cause of the effusion was malignancy. Other studies have shown similar results and, as the pleural ANA levels often mirror serum levels, the test is of limited diagnostic value.[108 112 113]

8.7 Pleural effusions in HIV infection

- **In patients with HIV infection, the differential diagnosis of pleural effusion is wide and differs from the immunocompetent patient.**

A pleural effusion is seen in 7–27% of hospitalised patients with HIV infection. Its three leading causes are Kaposi's sarcoma, parapneumonic effusions, and tuberculosis.[114] In one prospective study of 58 consecutive patients with HIV infection and radiographic evidence of a pleural effusion, the causes of the effusion were Kaposi's sarcoma in one third of the cases, parapneumonic effusion in 28%, tuberculosis in 14%, *Pneumocystis carinii* pneumonia in 10%, and lymphoma in a further 7%.[115]

In a large prospective series of 599 HIV infected patients over 3 years, 160 had a pleural effusion during an inpatient admission; 65% were small effusions, 23% moderate, and 13% large. In this series the most common cause was bacterial pneumonia and the overall in-hospital mortality was high at 10%.[116]

9 MANAGEMENT OF PERSISTENT UNDIAGNOSED PLEURAL EFFUSION

- **In persistently undiagnosed effusions the possibility of pulmonary embolism and tuberculosis should be reconsidered since these disorders are amenable to specific treatment. [C]**
- **Undiagnosed pleural malignancy proves to be the cause of many "undiagnosed" effusions with sustained observation.**

The cause of the pleural effusion is undetermined after repeated cytology and pleural biopsy in around 15% of cases.[39] It is sensible to reconsider diagnoses with a specific treatment—for example, tuberculosis, pulmonary embolism, fungal infection.[87] A tuberculin skin test is positive in about

Audit points

- The gross appearance of the pleural fluid and its odour should always be recorded.
- Pleural fluid pH should be performed in every case of suspected parapneumonic effusion.
- The diagnostic rate of pleural cytology should be audited.
- If the first pleural fluid cytology specimen is non-diagnostic, a second sample should be taken to increase the diagnostic yield.
- Pleural biopsy specimens should be placed in both saline and formalin and sent for histological examination and culture.
- Diagnostic bronchoscopy is not indicated in the assessment of an undiagnosed effusion unless the patient has haemoptysis or features suggestive of bronchial obstruction.

70% of patients with tuberculous pleurisy and the combination of a positive tuberculin skin test and an exudative pleural effusion containing predominantly lymphocytes is sufficient to justify empirical antituberculous therapy.[22] There are no specific pleural fluid tests for pulmonary embolism so, if there is a clinical suspicion of the diagnosis, imaging for embolism should be undertaken. Many undiagnosed pleural effusions are eventually proved to be due to malignancy. If this possibility is to be pursued after routine tests have failed, thoracoscopy is advised.

Authors' affiliations
N A Maskell, Oxford Centre for Respiratory Medicine, Churchill Hospital Site, Oxford Radcliffe Hospital, Headington, Oxford OX3 7LJ, UK
R J A Butland, Department of Thoracic Medicine, Gloucestershire Royal Hospital, Gloucester GL1 3NN, UK

REFERENCES

1 **Boutin C**, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. *Chest* 1995;**108**:754–8. [**Ib**]
2 **Scheurich JW**, Keuer SP, Graham DY. Pleural effusion: comparison of clinical judgment and Light's criteria in determining the cause. *South Med J* 1989;**82**:1487–91. [**IIb**]
3 **Light RW**. Pleural effusion due to pulmonary emboli. *Curr Opin Pulm Med* 2001;**7**:198–201. [**IV**]
4 **Chetty KG**. Transudative pleural effusions. *Clin Chest Med* 1985;**6**:49–54. [**IV**]
5 **Light RW**. Diagnostic principles in pleural disease. *Eur Respir J* 1997;**10**:476–81. [**IV**]
6 **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. [**IIb**]
7 **Boddington M**. Serous effusions. In: Coleman DV, ed. *Clinical cytotechnology*. London: Butterworths, 1989: 271–5. [**IV**]
8 **Sahn S**. Pleural fluid analysis: narrowing the differential diagnosis. *Semin Respir Med* 1987;**9**:22–9. [**IV**]
9 **Light RW**, Erozan YS, Ball WCJ. Cells in pleural fluid. Their value in differential diagnosis. *Arch Intern Med* 1973;**132**:854–60. [**III**]
10 **Light RW**, MacGregor MI, Luchsinger PC, *et al*. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972;**77**:507–13. [**III**]
11 **Gil S**, Martinez M, Cases V, *et al*. Pleural cholesterol in differentiating transudates and exudates. A prospective study of 232 cases. *Respiration* 1995;**62**:57–63. [**III**]
12 **Hamm H**, Brohan U, Bohmer R, *et al*. Cholesterol in pleural effusions. A diagnostic aid. *Chest* 1987;**92**:296–302. [**IV**]
13 **Ortega L**, Heredia JL, Armengol R, *et al*. The differential diagnosis between pleural exudates and transudates: the value of cholesterol. *Med Clin (Barc)* 1991;**96**:367–70. [**III**]
14 **Roth B**. The serum-effusion albumin gradient. *Chest* 1990;**98**:546–9. [**IV**]
15 **Heffner JE**, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Primary Study Investigators. *Chest* 1997;**111**:970–80. [**IIa**]
16 **Heffner JE**. Evaluating diagnostic tests in the pleural space. Differentiating transudates from exudates as a model. *Clin Chest Med* 1998;**19**:277–93. [**IV**]
17 **Light RW**. *Pleural diseases*. 3rd ed. Baltimore: Williams and Wilkins, 1995. [**III**]
18 **Wysenbeek AJ**, Lahav M, Aelion JA, *et al*. Eosinophilic pleural effusion: a review of 36 cases. *Respiration* 1985;**48**:73–6. [**III**]
19 **Adelman M**, Albelda SM, Gottlieb J, *et al*. Diagnostic utility of pleural fluid eosinophilia. *Am J Med* 1984;**77**:915–20. [**III**]
20 **Martinez-Garcia MA**, Cases-Viedma E, Cordero-Rodriguez PJ, *et al*. Diagnostic utility of eosinophils in the pleural fluid. *Eur Respir J* 2000;**15**:166–9. [**III**]
21 **Levine H**, Metzger W, Lacera D, *et al*. Diagnosis of tuberculous pleurisy by culture of pleural biopsy specimen. *Arch Intern Med* 1970;**126**:269–71. [**III**]
22 **Ansari T**, Idell S. Management of undiagnosed persistent pleural effusions. *Clin Chest Med* 1998;**19**:407–7. [**IV**]
23 **Light RW**, Rogers JT, Cheng D, *et al*. Large pleural effusions occurring after coronary artery bypass grafting. Cardiovascular Surgery Associates, PC. *Ann Intern Med* 1999;**130**:891–6. [**III**]
24 **Good JT Jr**, Taryle DA, Maulitz RM, *et al*. The diagnostic value of pleural fluid pH. *Chest* 1980;**78**:55–9. [**III**]
25 **Hamm H**, Light RW. Parapneumonic effusion and empyema. *Eur Respir J* 1997;**10**:1150–6. [**IV**]
26 **Heffner JE**, Brown LK, Barbieri C, *et al*. Pleural fluid chemical analysis in parapneumonic effusions. A meta-analysis. *Am J Respir Crit Care Med* 1995;**151**:1700–8. [**IIb**]
27 **Rodriguez P**, Lopez M. 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. [**IIb**]
28 **Sahn SA**, Good JTJ. Pleural fluid pH in malignant effusions. Diagnostic, prognostic, and therapeutic implications. *Ann Intern Med* 1988;**108**:345–9. [**IIb**]
29 **Sahn SA**. Pathogenesis and clinical features of disease associated with a low pleural fluid glucose. In: *The pleura in health and disease*. New York, 1985: 267–85. [**IV**]
30 **Light RW**, Ball WCJ. Glucose and amylase in pleural effusions. *JAMA* 1973;**225**:257–9. [**III**]
31 **Sahn SA**. The pleura. *Am Rev Respir Dis* 1988;**138**:184–234. [**IV**]
32 **Houston MC**. Pleural fluid pH: diagnostic, therapeutic, and prognostic value. *Am J Surg* 1987;**154**:333–7. [**IV**]
33 **Potts DE**, Willcox MA, Good JT Jr, *et al*. The acidosis of low-glucose pleural effusions. *Am Rev Respir Dis* 1978;**117**:665–71. [**IV**]
34 **Ende N**. Studies of amylase activity in pleural effusions and ascites. *Cancer* 1960;**13**:283–7. [**III**]
35 **Sherr HP**, Light RW, Merson MH, *et al*. Origin of pleural fluid amylase in esophageal rupture. *Ann Intern Med* 1972;**76**:985–6. [**IV**]
36 **Kramer M**. High amylase levels in neoplasm-related pleural effusion. *Ann Intern Med* 1989;**110**:567–9. [**IV**]
37 **Light RW**. Pleural effusions. *Med Clin North Am* 1977;**61**:1339–52. [**IV**]
38 **Lankisch PG**, Droge M, Becher R. Pleural effusions: a new negative prognostic parameter for acute pancreatitis. *Am J Gastroenterol* 1994;**89**:1849–51. [**IV**]
39 **Hirsch A**. Pleural effusion: laboratory tests in 300 cases. *Thorax* 1979;**34**:106–12. [**III**]
40 **Salyer WR**, Eggleston JC, Erozan YS. Efficacy of pleural needle biopsy and pleural fluid cytopathology in the diagnosis of malignant neoplasm involving the pleura. *Chest* 1975;**67**:536–9. [**IV**]
41 **Nance KV**, Shermer RW, Askin FB. Diagnostic efficacy of pleural biopsy as compared with that of pleural fluid examination. *Mod Pathol* 1991;**4**:320–4. [**III**]
42 **Prakash UB**, Reiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. *Mayo Clin Proc* 1985;**60**:158–64. [**IV**]
43 **Garcia L**. The value of multiple fluid specimens in the cytological diagnosis of malignancy. *Mod Pathol* 1994;**7**:665–8. [**III**]
44 **Dekker A**, Bupp PA. Cytology of serous effusions. An investigation into the usefulness of cell blocks versus smears. *Am J Clin Pathol* 1978;**70**:855–60. [**III**]
45 **Pettersson T**, Froseth B, Riska H, *et al*. Concentration of hyaluronic acid in pleural fluid as a diagnostic aid for malignant mesothelioma. *Chest* 1988;**94**:1037–9. [**III**]
46 **Whitaker D**. The cytology of malignant mesothelioma. *Cytopathology* 2000;**11**:139–51. [**IV**]
47 **Dejmek A**, Hjerpe A. Reactivity of six antibodies in effusions of mesothelioma, adenocarcinoma and mesotheliosis: stepwise logistic regression analysis. *Cytopathology* 2000;**11**:8–17. [**IIb**]
48 **Brown RW**, Clark GM, Tandon AK, *et al*. Multiple-marker immunohistochemical phenotypes distinguishing malignant pleural mesothelioma from pulmonary adenocarcinoma. *Hum Pathol* 1993;**24**:4–54. [**III**]
49 **Blackmore CC**, Black WC, Dallas RV, *et al*. Pleural fluid volume estimation: a chest radiograph prediction rule. *Acad Radiol* 1996;**3**:103–9. [**IV**]
50 **O'Moore PV**, Mueller PR, Simeone JF, *et al*. Sonographic guidance in diagnostic and therapeutic interventions in the pleural space. *AJR* 1987;**149**:1–5. [**IV**]
51 **Ruskin JA**, Gurney JW, Thorsen MK, *et al*. Detection of pleural effusions on supine chest radiographs. *AJR* 1987;**148**:681–3. [**III**]
52 **Armstrong P**, Wilson AG, Dee P, *et al*. *Imaging of diseases of the chest*. 3rd ed. Mosby, 2001. [**IV**]
53 **Eibenberger KL**, Dock WI, Ammann ME, *et al*. Quantification of pleural effusions: sonography versus radiography. *Radiology* 1994;**191**:681–4. [**III**]
54 **Gryminski J**, Krakowka P, Lypacewicz G. The diagnosis of pleural effusion by ultrasonic and radiologic techniques. *Chest* 1976;**70**:33–7. [**IV**]
55 **Yang PC**, Luh KT, Chang DB, *et al*. Value of sonography in determining the nature of pleural effusion: analysis of 320 cases. *AJR* 1992;**159**:29–33. [**IV**]

56 **Wu RG**, Yang PC, Kuo SH, *et al*. "Fluid color" sign: a useful indicator for discrimination between pleural thickening and pleural effusion. *J Ultrasound Med* 1995;**14**:767–9. [**III**]
57 **Wu RG**, Yuan A, Liaw YS, *et al*. Image comparison of real-time gray-scale ultrasound and color Doppler ultrasound for use in diagnosis of minimal pleural effusion. *Am J Respir Crit Care Med* 1994;**150**:510–4. [**IIb**]
58 **Lipscomb DJ**, Flower CD, Hadfield JW. Ultrasound of the pleura: an assessment of its clinical value. *Clin Radiol* 1981;**32**:289–90. [**IV**]
59 **McLoud TC**. CT and MR in pleural disease. *Clin Chest Med* 1998;**19**:261–76. [**IV**]
60 **Leung AN**, Muller NL, Miller RR. CT in differential diagnosis of diffuse pleural disease. *AJR* 1990;**154**:3–92. [**III**]
61 **Scott EM**. Diffuse pleural thickening: percutaneous CT-guided cutting needle biopsy. *Radiology* 1995;**194**:867–70. [**III**]
62 **Traill ZC**, Davies RJ, Gleeson FV. Thoracic computed tomography in patients with suspected malignant pleural effusions. *Clin Radiol* 2001;**56**:193–6. [**III**]
63 **Muller NL**. Imaging of the pleura. *Radiology* 1993;**186**:297–309. [**IV**]
64 **McLoud TC**, Flower CD. Imaging the pleura: sonography, CT, and MR imaging. *AJR* 1991;**156**:1145–53. [**IV**]
65 **Falaschi F**, Battolla L, Mascalchi M, *et al*. Usefulness of MR signal intensity in distinguishing benign from malignant pleural disease. *AJR* 1996;**166**:963–8. [**IIb**]
66 **Morrone N**, Algranti E, Barreto E. Pleural biopsy with Cope and Abrams needles. *Chest* 1987;**92**:1050–2. [**IIb**]
67 **Mungall IP**, Cowen PN, Cooke NT, *et al*. Multiple pleural biopsy with the Abrams needle. *Thorax* 1980;**35** :600–2. [**IV**]
68 **Tomlinson JR**. Closed pleural biopsy. A prospective study of dual biopsy sites. *Am Rev Respir Dis* 1900;**133**:56A. [**III**]
69 **Tomlinson JR**. Invasive procedures in the diagnosis of pleural disease. *Semin Respir Med* 1987;**9**:30– 6. [**IIb**]
70 **Sahn SA**. Pleural manifestations of pulmonary disease. *Hosp Pract Hosp Ed* 1981;**16**:73–9, 83. [**IV**]
71 **Escudero BC**, Garcia CM, Cuesta CB, *et al*. Cytologic and bacteriologic analysis of fluid and pleural biopsy specimens with Cope's needle. Study of 414 patients. *Arch Intern Med* 1990;**150**:1190–4. [**III**]
72 **Poe RH**, Israel RH, Utell MJ, *et al*. Sensitivity, specificity, and predictive values of closed pleural biopsy. *Arch Intern Med* 1984;**144**:325–8. [**III**]
73 **Chertien J**. *Needle pleural biopsy. The pleura in health and disease*. New York: Marcel Dekker, 1985: 631–42. [**IV**]
74 **McAleer JJ**, Murphy GJ, Quinn RJ. Needle biopsy of the pleura in the diagnosis of pleural effusion. *Ulster Med J* 1987;**56**:54–7. [**III**]
75 **Canto A**, Rivas J, Saumench J, *et al*. Points to consider when choosing a biopsy method in cases of pleurisy of unknown origin. *Chest* 1983;**84**:176–9. [**IV**]
76 **Maskell NA**, Gleeson FV, Davies RJO. Standard pleural biopsy versus CT-guided cutting-needle biopsy for the diagnosis of pleural malignancy in pleural effusions: A randomised controlled trial. *Lancet* 2003 (in press). [**IIa**]
77 **Adams RF**, Gleeson FV. Percutaneous image-guided cutting needle biopsy of the pleura in the diagnosis of malignant mesothelioma. *Chest* 2001;**120**:1798–802. [**III**]
78 **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. [**III**]
79 **Harris RJ**, Kavuru MS, Rice TW, *et al*. The diagnostic and therapeutic utility of thoracoscopy. A review. *Chest* 1995;**108**:828–41. [**IV**]
80 **Page RD**. Thoracosopy: a review of 121 consecutive surgical procedures. *Ann Thorac Surg* 1989;**48**:66–8. [**IV**]
81 **Loddenkemper R**. Thoracoscopy: state of the art. *Eur Respir J* 1998;**11**:213–21. [**IV**]
82 **Viskum K**, Enk B. Complications of thoracoscopy. *Poumon Coeur* 1981;**37**:25–8. [**IV**]
83 **Heaton RW**, Roberts CM. The role of fibreoptic bronchoscopy in the investigation of pleural effusion. *Postgrad Med J* 1988;**64**:581–2. [**IV**]
84 **Upham JW**, Mitchell CA, Armstrong JG, *et al*. Investigation of pleural effusion: the role of bronchoscopy. *Aust N Z J Med* 1992;**22**:41–3. [**III**]
85 **Feinsilver SH**, Barrows AA, Braman SS. Fiberoptic bronchoscopy and pleural effusion of unknown origin. *Chest* 1986;**90**:516–9. [**III**]
86 **Chang SC**, Perng RP. The role of fiberoptic bronchoscopy in evaluating the causes of pleural effusions. *Arch Intern Med* 1989;**149**:855–7. [**IIb**]
87 **Turton CW**. Troublesome pleural fluid. *Br J Dis Chest* 1987;**81**:217–24. [**IV**]
88 **Ferrer S**. Pleural tuberculosis: incidence, pathogenesis, diagnosis, and treatment. *Curr Opin Pulm Med* 1996;**2**:327–34. [**IV**]
89 **Hillerdal G**. Chylothorax and pseudochylothorax. *Eur Respir J* 1997;**10**:1150–6. [**IV**]
90 **Ferguson GC**. Cholesterol pleural effusion in rheumatoid lung disease. *Thorax* 1966;**21**:577–82. [**IV**]
91 **Hillerdal G**. Chyliform (cholesterol) pleural effusion. *Chest* 1985;**88**:426–8. [**IV**]
92 **Romero S**, Martin C, Hernandez L, *et al*. Chylothorax in cirrhosis of the liver: analysis of its frequency and clinical characteristics. *Chest* 1998;**114**:154–9. [**IV**]
93 **Berkman N**, Liss H, Kramer MR. Pyelonephritis as a cause of pleural effusion. *Respiration* 1996;**63**:384–6. [**IV**]
94 **Miller KS**, Wooten S, Sahn SA. Urinothorax: a cause of low pH transudative pleural effusions. *Am J Med* 1988;**85**:448–9. [**IV**]
95 **Stark DD**, Shanes JG, Baron RL, *et al*. Biochemical features of urinothorax. *Arch Intern Med* 1982;**142**:1509–11. [**IV**]
96 **Garcia-Pachon E**, Padilla-Navas I. Pleural effusion due to pyelonephritis or urinothorax? *Respiration* 1997;**64**:392. [**IV**]
97 **Berger HW**, Mejia E. Tuberculous pleurisy. *Chest* 1973;**63**:88–92. [**IV**]
98 **Idell S**. Evaluation of perplexing pleural effusions. *Ann Intern Med* 1994;**110**:567–9. [**IV**]
99 **Gakis C**. Adenosine deaminase (ADA) isoenzymes ADA1 and ADA2: diagnostic and biological role. *Eur Respir J* 1996;**9**:632–3. [**IV**]
100 **Valdes L**, Alvarez D, San Jose E, *et al*. Tuberculous pleurisy: a study of 254 patients. *Arch Intern Med* 1998;**158**:2017–21. [**III**]
101 **Burgess LJ**, Maritz FJ, Le Roux I, *et al*. Use of adenosine deaminase as a diagnostic tool for tuberculous pleurisy. *Thorax* 1995;**50**:672–4. [**IV**]
102 **van Keimpema AR**, Slaats EH, Wagenaar JP. Adenosine deaminase activity, not diagnostic for tuberculous pleurisy. *Eur J Respir Dis* 1987;**71**:15–8. [**IV**]
103 **Hsu WH**, Chiang CD, Huang PL. Diagnostic value of pleural adenosine deaminase in tuberculous effusions of immunocompromised hosts. *J Formos Med Assoc* 1993;**92**:668–70. [**III**]
104 **Epler GR**, McLoud TC, Gaensler EA. Prevalence and incidence of benign asbestos pleural effusion in a working population. *JAMA* 1982;**247**:617–22. [**IIb**]
105 **Hillerdal G**, Ozesmi M. Benign asbestos pleural effusion: 73 exudates in 60 patients. *Eur J Respir Dis* 1987;**71**:113–21. [**III**]
106 **Robinson BW**, Musk AW. Benign asbestos pleural effusion: diagnosis and course. *Thorax* 1981;**36**:896–900. [**III**]
107 **Joseph J**, Sahn SA. Connective tissue diseases and the pleura. *Chest* 1993;**104**:262–70. [**IV**]
108 **Pettersson T**, Klockars M, Hellstrom PE. Chemical and immunological features of pleural effusions: comparison between rheumatoid arthritis and other diseases. *Thorax* 1982;**37**:354–61. [**IV**]
109 **Hunder GG**, McDuffie FC, Huston KA, *et al*. Pleural fluid complement, complement conversion, and immune complexes in immunologic and non immunologic diseases. *J Lab Clin Med* 1977;**90**:971–80. [**IV**]
110 **Good JT Jr**, King TE, Antony VB, *et al*. Lupus pleuritis. Clinical features and pleural fluid characteristics with special reference to pleural fluid antinuclear antibodies. *Chest* 1983;**84**:714–8. [**IV**]
111 **Khare V**, Baethge B, Lang S, *et al*. Antinuclear antibodies in pleural fluid. *Chest* 1994;**106**:866–71. [**III**]
112 **Salomaa ER**, Viander M, Saaresranta T, *et al*. Complement components and their activation products in pleural fluid. *Chest* 1998;**114**:723–30. [**III**]
113 **Chandrasekhar AJ**. Antibody deposition in the pleura: a finding in drug-induced lupus. *J Allergy Clin Immunol* 1978;**61**:399–402. [**IV**]
114 **Afessa B**. Pleural effusions and pneumothoraces in AIDS. *Curr Opin Pulm Med* 2001;**7**:202–9. [**IV**]
115 **Miller RF**, Howling SJ, Reid AJ, *et al*. Pleural effusions in patients with AIDS. *Sex Transm Infect* 2000;**76**:122–5. [**IIb**]
116 **Afessa B**. Pleural effusion and pneumothorax in hospitalized patients with HIV infection: the pulmonary complications, ICU support, and prognostic factors of hospitalized patients with HIV (PIP) study. *Chest* 2000;**117**:1031–7. [**III**]