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

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. 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 3).

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. 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.

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. In contrast, an exudative pleural effusion develops when the pleural surface and/or the local capillary permeability are altered. 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)
Figure 1  Flow diagram of the investigation pathway for a unilateral pleural effusion of unknown aetiology.
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. 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. If it is still turbid, this is because of a high lipid content and a chylothorax or pseudochylothorax are likely. If it is still turbid 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. 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. Grossly bloody pleural fluid is usually due to malignancy, pulmonary embolus with infarction, trauma, benign asbestos pleural effusions, or post-cardiac injury syndrome (PCIS).

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). [C]

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. [C] The accuracy of these different indices

### 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. [D] Table 1 lists the characteristics of the pleural fluid in certain pleural diseases.

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### 5.3 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

### 5.4 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
- Urothorax
- Superior vena cava obstruction
- Ovarian hyperstimulation
- Meigs’ syndrome

### Table 1 Appearance of pleural fluid

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Suspected disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putrid odour</td>
<td>Anaerobic empyema</td>
</tr>
<tr>
<td>Food particles</td>
<td>Oesophageal rupture</td>
</tr>
<tr>
<td>Bile stained</td>
<td>Cholecystitis (biliary fistula)</td>
</tr>
<tr>
<td>Milky</td>
<td>Chylothorax (pleurochyllothorax)</td>
</tr>
<tr>
<td>“anchovy sauce” like fluid</td>
<td>Ruptured amoebic abscess</td>
</tr>
</tbody>
</table>

### Table 5 Causes of the pleural fluid

5.2 Differentiating between a pleural fluid exudate and transudate

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### Table 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 3 Causes of exudative pleural effusions

**Common causes**

- Malignancy
- Parapneumonic effusions

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- Rheumatoid arthritis
- Autoimmune diseases
- Benign asbestos effusion
- Pancreatitis
- Post-myocardial infarction syndrome

**Rare causes**

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- Drugs (see box 1)
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### Table 2 Causes of transudative pleural effusions

**Very common causes**

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**Rare causes**

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A pleural fluid pH of <7.2 with a normal blood pH is found in the same diagnoses as a low pleural fluid glucose. 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. 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.

A prospective study of the value of pH in malignant pleural effusions by Rodríguez and Lopez 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).

### 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. The lowest glucose concentrations are found in rheumatoid effusions and empyema. In pleural infection, pH discriminates better than glucose. 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).

### 5.6 Amylase
- Amylase measurement should be requested if acute pancreatitis or rupture of the oesophagus is possible.
- 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. This suggests acute pancreatitis, pancreatic pseudocyst, rupture of the oesophagus, ruptured ectopic pregnancy, or pleural malignancy (especially adenocarcinoma). Approximately 10% of malignant effusions have raised pleural amylase levels.

Iso-enzyme analysis can be useful in suspected cases of oesophageal rupture as this will show the amylase is of salivary origin. 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.

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.

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.

### 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.
- Both cell blocks and fluid smears should be prepared for examination and, if the fluid has clotted, it needs to be fixed and sectioned from a histological section.

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**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. 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”).

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.

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. Benign aetiologies include parapneumonic effusions, tuberculosis, drug induced pleurisy, benign asbestos pleural effusions, Churg-Strauss syndrome, pulmonary infarction, and parasitic disease. It is often the result of air or blood in the pleural cavity. However, malignancy is also a common cause; 11 of a series of 45 eosinophilic effusions were due to cancer.

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, as many as 10% of tuberculous pleural effusions are predominantly neutrophilic. Lymphoma, sarcoïdosis, rheumatoid disease, and chylothorax can cause a lymphocytic pleural effusion.

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.

#### 5.4 pH

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

Pleural fluid of air or blood in the pleural cavity. A pH of <7.2 is neutrophilic.

10% of tuberculous pleural effusions are predominantly less difficult to treat.

Non-bloody effusions tend to have small lymphocytes related to bleeding into the pleural cavity from the time of surgery. Non-bloody effusions were due to cancer.

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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. 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. A retrospective review of 414 patients between 1973 and 1982 compared the diagnostic efficacy of cytology alone and in combination with pleural biopsy. 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.

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

### 6 DIAGNOSTIC IMAGING

#### 6.1 Plain radiography

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

  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. Lateral decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating decubitus films are occasionally useful as free fluid gravitates to the most dependent part of the chest wall, differentiating...
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.

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 al66 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.64–66 At least four samples need to be taken to optimise diagnostic accuracy,77 and these should be taken from one site as dual biopsy sites do not increase positivity.64 The biopsy specimens should be placed in 10% formaldehyde for histological examination and sterile saline for tuberculous 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.60 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.7 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 contrast 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%). 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%). 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 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 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.

Complications of this procedure appear to be few. The most serious, but rare, is severe haemorrhage caused by blood vessel trauma. In a series of 566 examinations by Viskum and Enk 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 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 studied 245 patients over 2 years and Feinsilver et al 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 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.

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).

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. In the past, the most common causes of a pseudochylous effusion were tuberculosis and artificial pneumothorax. Chronic rheumatoid pleurisy is now the usual cause.

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).

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>
<thead>
<tr>
<th>Feature</th>
<th>Pseudochylothorax</th>
<th>Chylothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>&lt;0.56 mmol/l (50 mg/dl)</td>
<td>&gt;1.24 mmol/l (110 mg/dl)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&gt;5.18 mmol/l (200 mg/dl)</td>
<td>&lt;5.18 mmol/l (200 mg/dl)</td>
</tr>
<tr>
<td>Cholesterol crystals</td>
<td>Often present</td>
<td>Absent</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

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.
8.2 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. The pleural fluid smells like urine and resolves when the obstruction is removed. 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. [C]

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. The addition of pleural biopsy histology and culture improves the diagnostic rate to about 90%. The pleural fluid is a transudate and has a low pH. Pleural fluid can be serous, turbid, yellow green, milky, or haemorrhagic. 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% transudes; 80% are bloodstained. A pleural fluid red blood cell count of more than 100 000/mm$^3$ is suggestive of malignancy, pulmonary infarction, or trauma. Lower counts are unhelpful.

8.4 Pleural effusion due to pulmonary embolism

- There are no specific pleural fluid characteristics to distinguish those caused by pulmonary embolism. When pleural biopsies are taken, they should be sent for both histological examination and culture to improve the diagnostic sensitivity for tuberculosis. [B]

Pleural involvement occurs in 5% of patients with rheumatoid arthritis. The majority of patients with rheumatoid pleural effusions are men, even though the disease generally affects more women. The pleural fluid is a transudate and has a low pH. 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).

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. The effusion is usually small and asymptomatic, often with pleural fluid which is haemorrhagic. There is a propensity for the effusion to resolve within 6 months, leaving behind residual diffuse pleural thickening. 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).

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. 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%. 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%.

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. It is sensible to reconsider diagnoses with a specific treatment—for example, tuberculosis, pulmonary embolism, fungal infection. A tuberculin skin test is positive in about
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. There are no specific pleural fluid tests for pulmonary embolism so, if there is clinical suggestion 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.

### References


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

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