Pleural effusion: a structured approach to care†

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The accumulation of fluid in the pleural space is a common manifestation of a wide range of disease. This review provides a structured approach to the investigation of the patient with a pleural effusion. This should allow an accurate diagnosis to be made with the minimum number of invasive and time-consuming investigations.

Introduction

The accumulation of fluid in the pleural space is a common manifestation of a wide range of diseases, and frequently presents to general physicians. This review provides a structured approach to the investigation of the patient with a pleural effusion and details the key features of the most important causes. This approach should allow an accurate diagnosis to be made whilst exposing the patient to a minimum number of invasive and time-consuming investigations.

Pathophysiology

The pleural space normally contains 0.1–0.2 ml/kg body weight of fluid, filtered from systemic capillaries down a small pressure gradient. Fluid drains into the systemic circulation via a delicate network of lymphatics and eventually enters the mediastinal lymph nodes. Fluid may accumulate in the pleural space by a number of mechanisms: increased pulmonary capillary pressure, decreased (more negative) intrapleural pressure (e.g. atelectasis), decreased plasma oncotic pressure (e.g. hypoalbuminaemia), increased pleural membrane permeability and obstructed lymphatic flow (e.g. pleural malignancy or infection).1

Causes of pleural effusions

Pleural effusions are classified as transudates or exudates according to biochemical criteria (see later). Transudates are the result of changes in
hydrostatic forces, with capillary permeability remaining normal. Exudates involve increased capillary permeability and lymphatic obstruction. Table 1 lists the causes of transudative and exudative pleural effusions.

### Table 1 Causes of pleural effusions

<table>
<thead>
<tr>
<th>Transudate</th>
<th>Exudate</th>
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<tbody>
<tr>
<td><strong>Common causes</strong></td>
<td><strong>Malignancy – primary / secondary / mesothelioma</strong></td>
</tr>
<tr>
<td>• Left ventricular failure</td>
<td>• Parapneumonic effusion and empyema</td>
</tr>
<tr>
<td>• Cirrhotic liver disease</td>
<td>• Pulmonary embolus (with infarction)</td>
</tr>
<tr>
<td>• Hypoalbuminaemia</td>
<td>• Tuberculosis (TB)</td>
</tr>
<tr>
<td>• Atelectasis</td>
<td></td>
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<tr>
<td>• Peritoneal dialysis</td>
<td></td>
</tr>
<tr>
<td><strong>Less common causes</strong></td>
<td><strong>Rheumatoid arthritis</strong></td>
</tr>
<tr>
<td>• Pulmonary embolus (10–20% are transudates)</td>
<td>• SLE</td>
</tr>
<tr>
<td>• Malignancy (5% are transudates)</td>
<td>• Other connective tissue disease</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td>• Benign Asbestos Pleural Effusion (BAPE)</td>
</tr>
<tr>
<td>• Mitral stenosis</td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Constrictive pericarditis</td>
<td>• Oesophageal rupture</td>
</tr>
<tr>
<td>• Urinothorax</td>
<td>• After coronary artery bypass surgery</td>
</tr>
<tr>
<td>• Ovarian hyperstimulation</td>
<td>• Yellow nail syndrome</td>
</tr>
<tr>
<td>• Meig’s syndrome</td>
<td>• Drugs</td>
</tr>
<tr>
<td></td>
<td>• Fungal infections</td>
</tr>
<tr>
<td></td>
<td>• Chylothorax/pseudochylothorax</td>
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<tr>
<td></td>
<td>• Hydatid disease (ruptured cyst)</td>
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</table>

SLE, systemic lupus erythematosus; BAPE, benign asbestos pleural effusion.

**History and examination**

A thorough history may provide clues to aetiology and provides a measure of disability. Dyspnoea is a common and non-specific symptom; causes are multifactorial and reflect a combination of reduced chest wall compliance, depression of the diaphragm and reflexes stimulated by a reduction in lung volume. Chest pain implies involvement of the pleura, ribs or chest wall, suggesting an exudative process (e.g. malignancy, pleural infection, pulmonary infarction). Up to 75% of patients with effusions secondary to pulmonary emboli have a history of pleuritic pain, and dyspnoea is often out of proportion to the size of the effusion (which is usually less than one-third of a hemithorax).

Cough is also a non-specific symptom, although the production of purulent sputum suggests an infective aetiology. Constitutional symptoms such as weight loss, night sweats, anorexia and malaise may occur in association with pleural infection, tuberculous pleurisy or pleural malignancy. The presence of joint, skin or eye symptoms may suggest an
underlying connective tissue disease such as rheumatoid arthritis, which may first present as pleural effusion.

A drug history is essential as there is an ever-increasing list of drugs which may cause exudative effusions (more common examples include amiodarone, phenytoin, nitrofurantoin and methotrexate). The website www.pneumotox.com provides an exhaustive current list.

Given the increasing incidence of mesothelioma, a thorough occupational history from school-leaving age should be elicited. This should include the dates and amount of exposure to asbestos, circumstances and environment (e.g. ventilation, use of respiratory protection) and details of the employer (to aid subsequent compensation claims). High-risk occupations for asbestos exposure include construction, insulation, electrical repair, carpentry, plumbing, ship-building and petrochemical plant work. Some patients may not recall specific exposure, but an apparent absence of asbestos exposure does not exclude a diagnosis of mesothelioma.

Examination may confirm systemic features of malignancy or a connective tissue disease. A large effusion without evidence of contralateral tracheal shift may imply underlying lung cancer or mesothelioma.

A combination of history and clinical examination has been shown to identify the cause of a transudative effusion. Therefore in the correct clinical context and with supportive radiology, clinical assessment may obviate the need for immediate pleural fluid sampling. Pleural fluid analysis should be performed in the setting of a delayed response to treatment of the underlying cause, or if atypical features are present (such as fever, chest pain or unilaterally/disparately sized effusions in patients with left ventricular failure).

The chest radiograph

The erect PA chest radiograph is usually abnormal once >200 ml of fluid is present, whereas a lateral film will show blunting of the posterior costophrenic angle with as little as 50 ml. Pleural thickening can be distinguished from fluid by using a lateral decubitus film, as the freely moving fluid gravitates to the dependent part of the lung. Exudative effusions with loculation and fibrous septa may appear as mass lesions on the chest radiograph as fluid climbs into the fissure; ultrasound is helpful in this case. There may be difficulty identifying pleural effusions in the intensive care setting; supine films are less sensitive, and hazy opacification of one lung field or thickening of the minor fissure may be the only clues.

The chest radiograph may also identify other pathologies indicating the aetiology of the effusion (e.g. consolidation, tumour or pleural calcification). Massive effusions (complete or near-complete opacification) are most commonly malignant.
Pleural fluid analysis

Pleural fluid analysis is the most useful test in differentiating possible causes and directing further investigations. Therefore aspiration should be performed in all cases of radiologically confirmed pleural effusion, with the exception of cases where the clinical context is suggestive of a transudative process (see above). Current guidelines recommend the use of a fine bore (21g green) needle and a 50 ml syringe to gather an adequate sample (in obese subjects a longer needle may be necessary). In cases of pleural effusion of unknown aetiology all aspiration and biopsy sites should be marked with Indian ink, as local radiotherapy is recommended to prevent tumour invasion of the chest wall in patients who are subsequently diagnosed with mesothelioma.\textsuperscript{11}

The pleural fluid appearance following aspiration should be noted, as it may provide clues to the underlying diagnosis. Pleural fluid is commonly straw-coloured; this appearance is typical of transudates but also frequently occurs with exudative effusions. Blood-stained fluid is suggestive of malignancy, pulmonary infarction, trauma, benign asbestos pleural effusion (BAPE) or effusions occurring after coronary artery bypass surgery. A pleural fluid haematocrit >50\% of the individual’s peripheral blood haematocrit is diagnostic of a haemothorax. Aspiration of frank pus is diagnostic of empyema, and a putrid odour suggests anaerobic infection. Turbid pleural fluid may suggest empyema, although chylothorax may give rise to this appearance; the presence of a milky supernatant after centrifuging the sample implies chylothorax, whereas a clear supernatant (with clearance of cell debris) suggests empyema.\textsuperscript{12} The unusual finding of food particles in pleural fluid is diagnostic of oesophageal rupture.

Table 2 lists the recommended initial pleural fluid tests for effusions of unknown aetiology.

<table>
<thead>
<tr>
<th>Send for</th>
<th>Analyse</th>
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<tbody>
<tr>
<td><strong>Biochemistry</strong></td>
<td>Markers of capillary permeability</td>
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<tr>
<td></td>
<td>• Protein</td>
</tr>
<tr>
<td></td>
<td>• Lactate dehydrogenase (LDH)</td>
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<td></td>
<td>Markers of cell turnover/metabolism</td>
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<tr>
<td></td>
<td>• (pH)</td>
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<tr>
<td></td>
<td>• Glucose</td>
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<tr>
<td><strong>Cytology</strong></td>
<td>• Differential cell count</td>
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<tr>
<td></td>
<td>• Abnormal cells</td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
<td>• Gram stain and culture, acid-fast bacilli stains and culture</td>
</tr>
<tr>
<td></td>
<td>• Sending an additional sample in blood culture bottles may increase yield if pleural infection suspected</td>
</tr>
</tbody>
</table>
Biochemistry: transudate or exudate?

Pleural effusions are classified as transudates or exudates on the basis of the fluid protein level. Classically, a pleural fluid protein level >30g/l is an exudate and <30g/l is a transudate, in the context of a normal serum protein level. More stringent criteria (Light’s criteria given in Table 3) are required if the pleural fluid protein concentration is between 25 and 35g/l, or if the serum protein level is abnormal.13

A meta-analysis of 1448 patients showed Light’s criteria to be highly sensitive in identifying exudates.14 Rarely, they will erroneously identify an exudate in a patient with left ventricular failure on diuretics, but despite this they remain the most accurate way of differentiating exudate from transudate.

Glucose and pH

Bicarbonate accumulation in the pleural space means that normal pleural fluid pH is ~7.6. A substantial amount of lactic acid production is required to decrease the pleural pH to <7.3, as seen with metabolically active cells such as bacteria (empyema) or tumour (malignancy). The diffusion of glucose into and lactate out of the pleural space is impaired, decreasing pH further. Metabolic activity within the pleural space results in a low pleural fluid glucose (<3.3 mmol/l) and pH (<7.3) in the following situations: complicated parapneumonic effusions and empyema, malignancy, tuberculous pleuritis, oesophageal rupture, rheumatoid pleuritis and lupus pleuritis.15

The main use of pH is in the differentiation of simple parapneumonic effusion from complicated effusion or empyema (see later). This value changes immediate management and therefore should be measured on all pleural samples in suspected parapneumonic effusion. Substantial experience has shown that measurement of pH in non-purulent pleural fluid using standard blood gas analysers does not damage the machines, and it should be noted that testing pH with litmus paper is inaccurate.16 Local anaesthetic (such as lidocaine) is often used during pleural fluid sampling, and care must be taken as lidocaine is acidic. Some data suggest that pH <7.3 predicts poor survival17 and poor response to

<table>
<thead>
<tr>
<th>Table 3 Light’s criteria13</th>
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<tbody>
<tr>
<td>Pleural fluid is an exudate if one or more of the following criteria are met</td>
</tr>
<tr>
<td>1. Pleural fluid protein/serum protein &gt;0.5</td>
</tr>
<tr>
<td>2. Pleural fluid LDH/serum LDH&gt;0.6</td>
</tr>
<tr>
<td>3. Pleural fluid LDH more than two-thirds of the upper limit of normal serum LDH</td>
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</table>
pleurodesis in malignant effusions, but these results have not yet been reproduced. The lowest pleural fluid glucose levels are found in rheumatoid disease and empyema.

**Cell count**

The differential cell count in pleural aspirates can aid in narrowing the differential diagnosis. A predominance of polymorphonuclear cells reflects an acute process; in the context of consolidation on the chest radiograph, a parapneumonic effusion is most likely. Polymorphs are also seen in effusion caused by pulmonary embolus, tuberculosis and BAPE.

An eosinophilic pleural effusion (>10% eosinophils) is of little use in differentiating aetiology. It is often associated with air or blood in the pleural space, and does not exclude malignancy as a possible cause.

A lymphocytic pleural effusion is most often the result of tuberculosis or malignancy. However, up to 10% of tuberculosis effusions are polymorph predominant, and lymphocyte-rich exudates may also be caused by sarcoidosis, rheumatoid pleuritis and chylothorax.

**Cytology**

Pleural fluid sensitivity in diagnosing malignancy is variable, but it is an attractive option as it is fast and minimally invasive. Pooling the data from four large series with a total of 1370 patients showed that a diagnosis of malignancy was established from the first pleural aspiration cytology in 60% of cases. A second aspiration is warranted if the first is non-diagnostic, as the diagnosis may be confirmed in a further 27% of cases. A third attempt does not add useful diagnostic information.

**Specific tests**

Pleural fluid amylase levels are raised (pleural fluid levels higher than the normal range for serum or pleural-to-serum ratio >1) in oesophageal rupture, acute pancreatitis and malignancy (especially adenocarcinoma). Isoenzyme analysis differentiates oesophageal rupture from other causes, as amylase is of salivary origin in this context. Pleural fluid triglyceride and cholesterol levels should be measured in cases of suspected chylothorax and pseudochylothorax.

Adenosine
deaminase levels can be helpful in the diagnosis of tuberculous pleurisy (see below).

**Thoracic ultrasound scanning**

Thoracic ultrasound scanning (USS) has been shown to be more sensitive in estimating the amount of pleural fluid than chest radiography.\(^{25}\) USS also facilitates pleural fluid sampling in difficult cases (e.g. loculated effusions). USS-guided aspiration of pleural fluid is successful in up to 97% of cases,\(^9\) and is recommended if initial ‘blind’ aspiration is unsuccessful. USS can aid in the differentiation of transudates from exudates: those with septated and homogenously echogenic patterns are always exudates, whereas hypoechoic effusions may be either.\(^{26}\)

**Contrast-enhanced computed tomography (CT) scan**

If pleural aspiration is non-diagnostic, a contrast-enhanced CT is the investigation of choice and should ideally be performed prior to drainage of pleural fluid. Provided that the time delay is sufficient the pleural membrane can be visualized, allowing an assessment of pleural nodularity to be made.\(^{27}\) A high degree of specificity for malignant disease has been demonstrated in patients with nodular, mediastinal and parietal pleural thickening on CT scan.\(^{28}\) Circumferential thickening has a sensitivity as high as 100%, although the specificity is substantially less. The presence of pleural fluid also allows safer pleural biopsy under CT guidance.

In the context of parapneumonic effusion, the absence of pleural thickening is an important feature, as empyemas are associated with pleural thickening in 86–100% of cases.\(^{29}\) A parenchymal lung abscess is easily differentiated from empyema by thoracic CT: empyema commonly displays the ‘split pleura sign’, with lenticular opacification of the infected fluid.\(^{30}\)

CT scanning also allows assessment of the lungs and mediastinum, and may show unsuspected endobronchial disease or pleural plaques.

**Invasive tests**

**Pleural biopsy**

Blind pleural biopsy is typically performed using the Abrams needle in patients with at least moderately sized pleural effusions. At least
four biopsies should be taken from a single site, and the samples placed in sterile saline (for acid-fast bacilli smear and culture) and 10% formaldehyde (for histological examination). Complications are uncommon but include site pain, pneumothorax, vasovagal reactions and haematoma. If pneumothorax occurs, only a small minority require chest drain insertion (1%). Catastrophic haemorrhage occurs very rarely.\textsuperscript{21}

Image-guided biopsy has been shown to have a higher yield for tissue than blind biopsy, as areas of focal pleural thickening are identified and targeted. Furthermore, malignant pleural deposits often occur in the dependent parts of the lung (close to the midline and diaphragm) where they are poorly accessible with the Abrams needle because of reasonable safety concerns. In a direct comparison of the two techniques in a sample of 50 patients, CT-guided cutting-needle biopsy had a far higher sensitivity (87% versus 47%) with a specificity of 100%.\textsuperscript{31} Thus repeat biopsy is avoided in 40% of patients (and there are fewer passes) if CT-guided biopsy is used as the preliminary investigation. The complication rate of this technique is understandably lower, but a minority still experience haematoma and minor haemoptysis. Although image-guided biopsy is superior to Abrams biopsy in terms of safety and yield, it is not always readily available; Abrams biopsy remains useful, especially in cases of suspected tuberculosis.

**Thoracotomy**

The ‘gold standard’ for diagnosis of exudative pleural effusion is thoracotomy, which allows direct vision of the pleural surface, biopsy of areas which look abnormal and effective pleurodesis in one sitting. The diagnostic yield for malignancy is 80–95%, and in one study 66% of patients with a negative blind pleural biopsy achieved diagnosis at thoracoscopy.\textsuperscript{32} The procedure is mainly performed by surgeons in the UK, but is increasingly being used by respiratory physicians. The procedure is conducted under sedation with local anaesthetic, involving a short stay in hospital to allow full lung expansion post-procedure. This enables diagnosis and control of effusions in patients who may be unfit for a general anaesthetic and are unsuitable for surgery (e.g. video-assisted thoracoscopic surgery or minithoracotomy).

** Bronchoscopy**

Bronchoscopy has no role in the investigation of unexplained pleural effusion unless there are specific features indicating an endobronchial process such as an obstructing tumour.\textsuperscript{33} This will usually be detected on CT, hence the importance of this investigation in the work-up.
Treatment of pleural effusion

Treatment of pleural effusion is directed at identifying the cause and treating the underlying disease process. Transudative effusions characteristically resolve following treatment of their cause, whereas exudative effusions often require removal of fluid for symptomatic relief. This can be performed with simple thoracentesis, and intercostal chest drain insertion is often unnecessary. Exceptions include complex parapneumonic effusion and empyema, which only rarely resolve without intercostal drainage, and recurrent malignant effusions, where chest drainage permits the use of intrapleural pleurodesis agents (e.g. talc).

Specific causes of pleural effusion

Parapneumonic effusion and empyema

Pneumonia is associated with an exudative pleural effusion in up to 57% of cases and is the most common cause of pleural effusion in young patients. The majority resolve with antibiotic treatment, but a certain number will progress to an infected pleural space. The mortality of empyema is as high as 15% and up to 40% of these patients require surgery because medical treatment has failed. Therefore rapid recognition of such patients is important.

Pleural fluid progresses through an exudative phase (‘simple parapneumonic effusion’) to a fibrinopurulent stage, eventually resulting in an organizing stage with fibrotic scar tissue formation. In the early fibrinopurulent stage the fluid is termed ‘complicated parapneumonic effusion’, and pus in the pleural cavity is termed empyema. Each of these stages has a characteristic biochemical profile which guides management (Table 4).

Table 4 Characteristics of parapneumonic effusions and empyema

<table>
<thead>
<tr>
<th>Effusion type</th>
<th>Description</th>
<th>Biochemistry/microbiology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple parapneumonic effusion</td>
<td>Uninfected fluid with clear appearance</td>
<td>Normal pH, Normal LDH, Normal glucose, No organisms</td>
<td>Majority resolve with antibiotics alone, Drainage not usually required</td>
</tr>
<tr>
<td>Complicated parapneumonic effusion</td>
<td>Infected but non-purulent fluid</td>
<td>pH &lt; 7.2, glucose &lt; 2.2 mmol/l, LDH &gt; 1000 IU/l, Gram stain/culture may be positive</td>
<td>Drainage required for resolution</td>
</tr>
<tr>
<td>Empyema</td>
<td>Pus in pleural space</td>
<td>Gram stain/culture may be positive</td>
<td>Drainage required for resolution</td>
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</table>
A chest radiograph showing effusion and consolidation should raise the possibility of empyema. Patients with pneumonia not responding to antibiotics should be assessed for the presence of pleural infection. CT scanning can help differentiate empyema from intra-parenchymal masses, abscess and pleural thickening. All patients with suspected parapneumonic effusion should undergo diagnostic pleural fluid sampling, with USS guidance in cases of small or loculated effusions or if initial ‘blind’ attempts are unsuccessful. Empyema may present as an indolent illness with constitutional symptoms and be confused with malignancy.

The bacteriology of pleural infection varies, and there are significant differences between community- and hospital-acquired infection. Common causes of community-acquired infection in the UK include the Streptococcus milleri group (including *S.intermedius*, *S.constellatus* and *S.inonia*), *Streptococcus pneumoniae* and staphylococci, sometimes with associated anaerobes. Rarer organisms responsible include other streptococci, enterobacteria, *Haemophilus influenzae*, *Pseudomonas* spp., tuberculosis and *Nocardia*. Hospital-acquired infection (following pneumonia, surgery, trauma or pleural procedures) is frequently caused by methicillin-resistant *Staphylococcus aureus* (MRSA), staphylococci, enterobacteria or *Enterococcus*.35

Choice of antibiotic should be informed by the results of blood and pleural fluid cultures and sensitivities; empirical anaerobic antibiotic cover should be considered as anaerobes frequently coexist but are difficult to isolate. Possible treatments for community-acquired empyema include a second-generation cephalosporin (e.g. cefuroxime) or amnopenicillin intravenously plus anaerobic cover (e.g. metronidazole). In hospital-acquired empyema, treatment for aerobic Gram-positive, Gram-negative and anaerobic organisms is needed; choices include carbapenems, antipseudomonal penicillins or third-generation cephalosporins (e.g. ceftazidime) with metronidazole.

Patients with pleural infection are commonly malnourished and appropriate nutritional support is important. Surgical intervention is frequently necessary in patients who fail to improve with medical management alone; however, the optimal timing and nature of surgery is unknown. The recent joint MRC–BTS MIST trial demonstrated no mortality benefit or decreased need for surgery with the use of intrapleural streptokinase, and therefore the use of intrapleural fibrinolytics is not recommended.

**Malignancy**

Malignancy is the most common cause of exudative pleural effusions in patients aged >60 years. The majority are the result of metastases to the pleura from primaries in the lung (38%), breast (17%), lym-
Pleural effusion

Phoma (12%) and genitourinary tract (9%). The primary is unknown in 7–15% of cases. Malignant pleural effusion implies disseminated disease, and median survival depends upon the site and stage of the primary tumour (3–12 months, with the shortest in lung and the longest in breast primaries). Up to 25% of patients are asymptomatic at presentation.

Management rests upon treatment of the underlying cancer with chemotherapy or hormonal agents (in the case of breast and prostate primary). In symptomatic effusion drainage of the pleural space via a chest drain and subsequent pleurodesis is recommended. There are a number of pleurodesis agents, with the best evidence for sterile fine talc (4 g talc instilled in a slurry with local anaesthetic). This achieves up to 90% success (i.e. no recurrence of effusion). Pleuritic chest pain and fever are common side effects, with rare but serious side effects including adult respiratory distress syndrome or acute pneumonitis leading to respiratory compromise. Tetracycline (1.0–1.5 g or 20 mg/kg) is an alternative agent; it is less successful than talc but is associated with lower adverse effect rates, and therefore may be chosen for frailer patients.

Thoracoscopy is an option in patients with good performance status whose effusions are not controlled with chest-drain-instilled pleurodesis. Talc poudrage at thoracoscopy has a success rate >90%.

If tumour has seeded to both the visceral and parietal pleura the lung may be unable to expand, despite full pleural fluid drainage; this condition is known as ‘trapped lung’. Pleurodesis is often unsuccessful in such cases; if re-accumulation of fluid is troublesome, long-term tunnelled pleural catheters can be inserted. This option is limited to those patients able to drain their effusions periodically via a catheter, for which specific systems have been designed. Pleuroperitoneal shunting is a further option in a small minority of patients with trapped lung, but it requires surgical intervention.

Mesothelioma

Mesothelioma is a malignant tumour of the pleura and peritoneum, usually caused by previous asbestos exposure. There is a lag time of 15–40 years between exposure and disease presentation. The incidence has been increasing since the 1960s and is projected to reach a peak of more than 3000 cases per year in the UK in 2020. Most individuals in the UK were exposed in the 1940s; hence mesothelioma may increase to account for >1% of deaths amongst men in this age group.

The diagnosis should be considered in all patients with pleural effusions, especially in the context of pleural thickening, pleural plaques or chest pain. The initial history must include a thorough occupational history,
as this may have subsequent medicolegal implications. A history of asbestos exposure is elicited in up to 90% of patients; hence absence of exposure history does not exclude the diagnosis.38

Pleural fluid cytology is insensitive for the diagnosis of mesothelioma, although it may reveal other malignant cell types. As mesothelioma has a tendency to invade needle tracts, definitive diagnostic techniques (e.g. image-guided or thoracoscopic biopsy) should be used as early as possible in suspected cases. Pleural procedure sites should be marked with Indian ink to allow subsequent irradiation. Tumour seeding of the biopsy tract has been shown in up to 40% of such patients, and this strategy prevents this painful and unnecessary complication.11

Treatment comprises best supportive care, including control of recurrent effusions with pleurodesis.38 A small minority of patients with good prognostic features may be considered for surgery, although there is as yet no published evidence in support of this. Palliative radiotherapy is useful for local pain and invasion, and patients can be entered into trials for experimental chemotherapy. Prognosis is poor, with median survival of 8–14 months.38 Patients are eligible for compensation and all patient deaths must be reported to the coroner.

**Tuberculosis**

Pleural effusion due to tuberculosis develops from a delayed hypersensitivity reaction to mycobacteria in the pleural space following rupture of a subpleural caseous focus, and is common in areas of tuberculosis endemicity. Tuberculous pleurisy may occur during primary infection, when it tends to affect younger individuals in areas with a high prevalence of tuberculosis, or it may be recognized as a manifestation of disease reactivation, particularly affecting older patients. Lack of sensitivity renders tuberculin skin tests of limited use in the investigation of tuberculous pleurisy, particularly in HIV-infected patients. Pleural fluid is usually a serous exudate, and pleural fluid glucose and pH values are lowered in a minority of patients. Pleural fluid lymphocytosis is a typical finding, although a neutrophilia may be observed early in the disease course. In order to achieve a definitive diagnosis of tuberculous pleurisy, *Mycobacterium tuberculosis* must be isolated from the culture of pleural fluid or tissue; the presence of granulomas in pleural tissue is suggestive.39 Pleural tissue is typically obtained using an Abrams biopsy technique. Studies have reported variable results for the diagnosis of tuberculous pleurisy; reported sensitivities range from 10% to 47% for pleural fluid culture,30–43 39% to 84% for pleural biopsy histology30–43 and 56% to 82% for pleural biopsy culture.40,42 Combined culture and histology of pleural biopsy specimens has a greater diagnostic yield than histology alone.40
The use of biochemical markers such as adenosine deaminase (ADA) in pleural fluid may be of benefit in the early diagnosis of tuberculous pleurisy. Pleural fluid ADA levels are high in pleural tuberculosis, although an elevated value is non-specific and may occur in other infection and malignancy. The value of ADA measurement depends on both the local prevalence of tuberculosis and the likelihood of an alternative diagnosis. In areas where tuberculosis is prevalent, an elevated ADA value is both highly sensitive and specific, especially in young patients in whom empyema has been excluded, and treatment without pleural biopsy may be considered. An elevated ADA level is less useful in the elderly and in regions where tuberculosis is uncommon, as the possibility of an alternative diagnoses is increased; however, a low ADA value may still be informative as it makes tuberculosis unlikely.

Although tuberculous pleural effusions typically resolve spontaneously over several months, treatment is recommended as 65% of untreated patients develop active pulmonary tuberculosis within 5 years. Drug treatment of tuberculous pleurisy is the same as for pulmonary tuberculosis. The precise role of steroids in the treatment of tuberculous pleurisy remains uncertain; steroids may hasten both the improvement of clinical symptoms and the absorption of pleural fluid, although this has not been found in all studies. Further research is needed to clarify the effect of steroids on mortality or lung function following treatment.

**Connective tissue and autoimmune disease**

Rheumatoid arthritis affects the pleura in up to 5% of cases and, in keeping with other extra-articular manifestations of the disease, is more common in men. The fluid may be of various colours including green, turbid and haemorrhagic. Rheumatoid effusions characteristically have a low glucose and pH. If the pleural fluid glucose is >1.6 mmol/l, rheumatoid is an unlikely cause. Measurement of rheumatoid factor is unhelpful as pleural fluid levels reflect serum levels and, although it is often raised in rheumatoid effusions, it may also be increased in other aetiologies. Effusion and pleuritis secondary to rheumatoid arthritis often do not require treatment, resolving spontaneously over a period of months. Non-steroidal anti-inflammatory drugs can be used, and one case report supports the use of intrapleural corticosteroids in resistant cases.

The pleura is often involved in systemic lupus erythematosus (SLE), and the presence of lupus erythematosus cells in pleural fluid is diagnostic. Again, antinuclear antibodies reflect serum levels and are usually not useful diagnostically.
Chylothorax/pseudochylothorax

Chylothorax results from disruption of the thoracic duct, usually because of malignancy or trauma, and results in a ‘true’ chylous effusion. Pseudochylothorax (also known as cholesterol pleurisy) results from accumulation of cholesterol in a long-standing effusion of any cause, and is usually seen in rheumatoid or tuberculous pleurisy.

In chylothorax the triglyceride level is high (>1.24 mmol/l and not <0.56 mmol/l) and the presence of chylomicrons confirms this. In pseudochylothorax the cholesterol level is high (>5.18) and cholesterol crystals are often seen.

Treatment of chylothorax can be difficult and depends upon aetiology. Intercostal drainage and bowel rest (sometimes using parenteral nutrition) are used in cases of traumatic chylothorax, whereas chylothorax secondary to malignancy may respond to systemic chemotherapy or radiotherapy. Chylothorax in the postoperative patient can be particularly difficult to manage, with an associated high mortality.

Chylothorax is seen in patients with pulmonary lymphangioleiomyomatosis (LAM). In a recent series of 79 patients with LAM, 10% had chylothorax over a 25-year period. The size and progress of these chylothoraces was highly variable, with three patients managed with thoracocentesis alone, three managed with chemical pleurodesis and one who underwent thoracotomy and surgical pleurectomy. Effusions in this context may also respond to a medium-chain fatty acid diet, although this is often unpalatable.

Hydatid disease

In the developing world and in patients from rural farming communities, pleural effusion and infection secondary to hydatid disease should be considered. Hydatid is caused by infection with larva of the tapeworm Echinococcus (E. granulosus and E. multilocularis), the adult form of which lives in dogs and sheep. In humans, hydatid cysts are most often found in liver (60–70%) and lung (30–40%). Lung cysts may be associated with pleural abnormalities, and cyst rupture may result in hydropneumothorax and empyema. In a large series of patients from Turkey operated on for pulmonary hydatid disease, only 6% had pleural abnormalities. More than half of these cases had uncomplicated exudative effusions and only a small number had hydropneumothorax or empyema (1.7% and 0.8%, respectively, of the total number of patients). Hence pleural involvement and frank empyema are rare in hydatid disease, but it should remain in the differential given its high prevalence.

Diagnosis rests upon a combination of imaging and serology, with lung cysts well visualized on thoracic CT. Several serological tests are
available, but tend to have low sensitivity for lung involvement (65% of lung cysts associated with positive serology). Aspiration and biopsy under image guidance are possible, but carry the risk of spilling highly antigenic content into the systemic circulation. Treatment for cystic disease is usually a combination of surgical resection and albendazole.

The persistently undiagnosed pleural effusion

Despite repeated pleural fluid sampling and pleural biopsy, the aetiology of pleural effusion remains unknown in up to 15% of patients. As there are no specific pleural tests for pulmonary embolus, and this disease is amenable to specific treatment, further investigation with CT pulmonary angiography should be considered. Tuberculosis is similarly amenable to specific treatment and so should be reconsidered as a possible cause. The presence of a lymphocyte-rich exudative effusion in the correct clinical context may support a trial of empirical therapy for tuberculosis. In practice, many patients with undiagnosed effusions turn out to have malignancy.

References