Pleural Effusion

The lungs are covered by a thin serous layer (the visceral pleura). The pleura is then reflected on to the chest wall and pericardium (the parietal pleura). The lung hila ‘connect’ the visceral and parietal pleura. There is normally a small amount of fluid in the ‘pleural space’ between the parietal and visceral pleura, which lubricates movement between them. A pleural effusion occurs when the volume of this fluid is substantially greater than normal.

Aetiology

- When a pleural effusion is present, it is caused by disease which can be pulmonary, pleural or extrapulmonary.
- Approximately 40,000 people per year in the UK are affected by malignant pleural effusion and it is associated with significant morbidity and an overall poor prognosis. [1]
- Lung cancer (40%) and breast cancer (25%) are the most common metastatic tumours to the pleura. About 10% of all malignant pleural effusions are due to primary cancers arising from the pleura with malignant mesothelioma the predominant type (>90%) and cancer of unknown primary in less than 10%. [2]
- Benign pleural effusions are twice as common as malignant effusions. [3]
- Effusions are usually classified as either transudates or exudates. [4] However, blood (haemothorax), pus (empyema) or chyle (chylothorax) can also accumulate in the pleural space:
  - A transudative pleural effusion occurs when there is disruption of the hydrostatic and oncotic forces operating across the pleural membranes.
  - An exudative pleural effusion occurs when there is increased permeability of the pleural surface and/or capillaries, usually as a result of inflammation.
- Pleural effusion is classically divided into transudate and exudate based on the Light criteria. The Light criteria consist of measurement of the lactate dehydrogenase (LDH) and protein concentration in the pleural fluid and serum. Fluid is considered exudative if one of the following criteria is present: [5]
  - Pleural fluid-to-serum protein ratio >0.5; or
  - Pleural fluid-to-serum LDH ratio >0.6; or
  - Pleural fluid LDH concentration > two thirds upper limit of normal for serum LDH.
- Impaired lymphatic drainage and abnormal sites of entry (for example, passage of fluid across the diaphragm in people with ascites) can also be underlying causes of pleural effusions.

Causes of transudates [6]

Most common causes:

- Heart failure.
- Cirrhosis.
- Hypoalbuminaemia.
- Peritoneal dialysis.

Less common causes:

- Hypothyroidism.
- Nephrotic syndrome.
- Mitral stenosis.
- Pulmonary embolism (tends to produce a comparatively small effusion but disproportionate dyspnoea and pleuritic pain; 80% are exudates, 20% are transudates).
Rare causes:
- Superior vena cava obstruction (usually due to lung cancer).
- Constrictive pericarditis.
- Ovarian hyperstimulation.
- Meigs' syndrome (benign ovarian tumour, ascites and pleural effusion).

Causes of exudates\[6\]

Common causes:
- Pneumonia.
- Malignancy (most commonly, lung cancer in men and breast cancer in women; large unilateral pleural effusions are most commonly due to malignancy). [6, 7]

Less common causes:
- Pulmonary infarction (usually resulting from pulmonary embolism).
- Autoimmune disease, especially rheumatoid arthritis.
- Asbestos exposure.
- Pancreatitis.
- Complication of acute myocardial infarction (Dressler's syndrome).
- Tuberculosis (TB). [8]

Rare causes:
- Yellow nail syndrome (yellow nails, lymphoedema, pleural effusion and bronchiectasis).
- Adverse drug reactions (the most common are methotrexate, amiodarone, nitrofurantoin and phenytoin).
- Fungal infections.

Causes of chylothorax\[6\]

This is the presence of chyle in the pleural space. It usually occurs because of disruption of the thoracic duct. Causes include:
- Neoplasm: lymphoma, metastatic carcinoma.
- Trauma: operative and penetrating injuries.
- TB, sarcoidosis, cirrhosis, amyloidosis.

Causes of pseudochylothorax\[6\]

This is the accumulation of cholesterol crystals in a long-standing pleural effusion. Causes include:
- TB.
- Rheumatoid arthritis.
- Poorly treated empyema.

History
- An effusion has to be quite large before it causes any symptoms. Most malignant effusions are symptomatic.
- Symptoms may include shortness of breath (especially on exertion), cough and pleuritic chest pain. [9]
- Look for other features in the history: loss of weight may suggest malignancy; smoking history and haemoptysis can suggest lung cancer; there may be a history of another malignancy.
- Also note past medical history, drug history and occupational history (asbestos exposure). [10]
Examination

See separate Respiratory System History and Examination article. If the effusion is small, there may be no abnormality on examination.

- **Inspection** - note:
  - Any evidence of loss of weight or underlying malignancy.
  - Nicotine staining on the fingers.
  - Finger clubbing.
  - Rheumatoid changes in the hands.
  - Whether the patient is dyspnoeic.
  - Whether accessory muscles of respiration are being used.
  - If the effusion is unilateral and large - there will be reduced movement on that side of the chest.

- **Palpation** - chest expansion is reduced on the side of the effusion. Feel for deviation of the trachea. With a large unilateral effusion it is displaced away from the lesion. If there is associated collapse, the trachea is deviated towards the lesion. Mediastinal shift suggests an effusion that is in excess of a litre. There may be decreased tactile vocal fremitus.

- **Percussion** - an effusion will cause stony dullness on percussion. Laterally, it may rise up towards the axilla.

- **Auscultation** - breath sounds are diminished or absent over an effusion. Vocal resonance is lost over a pleural effusion except at its upper surface (this is called aegophony - it sounds like a goat bleating).

Investigations

**CXR**: this is the first investigation if a pleural effusion is suspected clinically.[11] PA film will usually suffice and, rarely, lateral views are needed. About 200 ml of fluid is required to be visible on a PA view but just 50 ml will cause costophrenic blunting on a lateral view.

Bilateral effusions with an enlarged heart shadow are commonly caused by congestive cardiac failure. Pleural plaques and calcifications may be seen, suggesting history of asbestos exposure.

Further initial investigations include ultrasound, CT scans, MRI and pleural fluid analysis.[12] Ultrasound is much more sensitive than CXRs for detecting pleural effusions and can detect even very small effusions.[13]

**Unilateral pleural effusion**
The British Thoracic Society (BTS) suggests a diagnostic algorithm for the investigation of a unilateral pleural effusion.[6] This is outlined below:

- **Does the clinical picture suggest a transudate (eg, left ventricular failure (LVF), hypoalbuminaemia, dialysis)?** It is often possible to identify transudative effusions by clinical assessment alone:
  - **If YES**, treat the cause. This may result in resolution. If it doesn't, continue with pleural aspiration, as below.
  - **If NO**, perform pleural aspiration. See separate Pleural Effusion Aspiration article. Ultrasound-guided pleural aspiration may be needed if the effusion is small or loculated.

- **Pleural aspiration (thoracentesis)**: send aspirated fluid for cytology; protein; lactate dehydrogenase (LDH); pH; Gram stain, culture and sensitivity; acid-alcohol fast bacilli (AAFB) stains and culture.

- **Do you suspect an empyema, chylothorax or haemothorax (because of the appearance/odour of the fluid)?**: If YES, perform additional pleural fluid tests:
  - For empyema: centrifuge to differentiate from chylothorax.
  - For chylothorax: cholesterol and triglyceride levels; centrifuge; presence of cholesterol crystals and chylomicrons.
  - For haemothorax: haematocrit.

- **Perform other tests as appropriate**: for example, blood tests (ESR, CRP, albumin, amylase, TFTs, blood culture). D-dimer and spiral CT are the best investigations if pulmonary embolism is suspected.

- **Wait for the results of the pleural aspiration**:
  - If the fluid analysis and chemical features have not given a diagnosis, referral to a chest physician should be made. They can then commence further investigations including:
    - **CT of the thorax ± abdomen**: usually carried out with contrast enhancement. This should be done before the effusion is drained and it has a high sensitivity for malignant pleural disease.[7] It can also show abdominal malignancy.
    - **Pleural biopsy**: samples should be sent for histology and TB culture; in mesothelioma, the biopsy site should be irradiated to stop biopsy site invasion by tumour. This can either be blind biopsy using an Abram’s needle, CT-guided biopsy or biopsy performed at the time of thoracoscopy.
    - **Repeat pleural aspiration**: special tests for rheumatoid disease (glucose and complement) and pancreatitis (amylase) may also be added.
    - **Thoracoscopy**: this allows direct visualisation of the pleura and can allow tissue diagnosis, fluid drainage and pleurectomy. It can be performed under conscious sedation.[14]
    - **Bronchoscopy**: BTS guidelines suggest that this investigation should be reserved for patients whose radiology suggests a mass or loss of volume or when there is a history of haemoptysis or possible foreign body aspiration.
Bilateral pleural effusion
The BTS suggests that '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'.[6]

Interpreting pleural fluid results

- **Transudate or exudate**: the pleural protein content usually differentiates between a transudative and an exudative effusion.

> Exudates have a protein level of >30 g/L; transudates have a protein level of <30 g/L.

If the pleural fluid protein is between 25 and 35 g/L, Light's criteria should be applied to differentiate transudates and exudates accurately.[6]

> Light's criteria state that the pleural fluid is an exudate if one or more of the following criteria are met:[6]
  - 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.

- **Bloody pleural fluid**: bloody pleural fluid can be caused by:
  - Malignancy.
  - Pulmonary embolus with infarction.
  - Trauma.
  - Benign asbestos pleural effusions.
  - Post-cardiac injury syndrome.

- **Pleural fluid haematocrit**: if the pleural fluid is bloody, the haematocrit of the fluid should be measured. 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 of the pleural fluid is <1%, the blood in the pleural fluid is not significant.[11]

- **pH**: pleural pH is mainly used to identify pleural infection. Normal pleural pH is about 7.6; a pH of <7.2 with a normal blood pH is found in:
  - Pleural infection and empyema.
  - Rheumatoid disease and systemic lupus erythematosus (SLE).
  - TB.
  - Malignancy.
  - Oesophageal rupture.

- **Cytology**: malignant effusions are diagnosed by pleural fluid cytology alone in only 60% of cases.[6] If the first pleural fluid cytology specimen is negative, it should be repeated.

- **Cholesterol, triglycerides, cholesterol crystals and chylomicrons**:
  - Chylothorax usually has a triglyceride level >1.24 mmol/L, cholesterol <5.18 mmol/L, no cholesterol crystals and the presence of chylomicrons.
  - Pseudochylothorax has a triglyceride level <0.56 mmol/L, cholesterol level >5.18 mmol/L, no chylomicrons and the presence of cholesterol crystals.

- **Glucose**: causes of low pleural glucose levels (<3.3 mmol/L) are:
  - Empyema.
  - Rheumatoid disease.
  - SLE.
  - TB.
  - Malignancy.
  - Oesophageal rupture.

- **Differential white cell counts**: pleural lymphocytosis is common in malignancy and TB.

Management

- Management should be aimed at the underlying disease. If a transudate is confirmed, aspiration should be avoided.
- Small effusions that are not causing respiratory embarrassment may be managed by observation.
- Tapping the fluid can give symptomatic relief as well as being useful for diagnosis but the effusion is likely to re-form. Repeated tapping may be used in palliative care.
- No more than 1.5 litres should be removed at a single procedure, as fluid shifts can result in pulmonary oedema.[15]
- In malignant effusions, if no attempt is made at pleurodesis, nearly all have recurred within a month.
- A chest drain can also be inserted for controlled drainage of the effusion. The drain can be removed if/when the underlying disease has been treated. Chest drains are often needed for the management of empyema and haemothorax.
- Long-term indwelling pleural drainage may be used in some patients with malignant effusions.
- Pleurectomy is also used in some cases of malignant effusion when other treatment options have failed.
- Surgically implanted pleuroperitoneal shunts are occasionally used for the treatment of malignant effusions and chylothorax.

**Pleurodesis**
- This is injection of a sclerosant to cause adhesion of the visceral and parietal pleura and to help to prevent reaccumulation of the effusion. Sclerosing agents that are commonly used include tetracycline, sterile talc and bleomycin.
- It is most often used in the management of recurrent malignant effusions.
- For more detail on how to carry out the procedure, refer to the BTS guidelines for the management of malignant pleural effusions.[6]

**Prognosis**
- This is dependent on the cause of the effusion.
- The presence of a malignant pleural effusion is associated with a poor prognosis with median survival following diagnosis ranging from 3 to 12 months depending on cell type.[1]

**Further reading & references**
6. Pleural Disease Guidelines; British Thoracic Society (September 2010)

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