

Managing Pleural Disease in Acute Medicine (I): Pleural Effusion

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Key Learning Points

- Light's criteria remain the best method to differentiate exudates from transudates.
- Patients presenting with bilateral pleural effusions which are likely to be transudative do not need diagnostic pleural aspiration unless atypical features are present.
- Inoculation of blood culture bottles improves diagnostic yield in suspected pleural infection.
- Mycobacterial culture of pleural fluid in suspected tuberculosis is unlikely to give positive cultures. Pleural biopsy and ADA/interferon assay are required to increase the likelihood of diagnosis.
- Developments in diagnostic markers, such as NT-proBNP, pneumococcal antigen and mesothelin, may improve diagnostic yields from pleural fluid analysis in the future.

Abstract

A pleural effusion is the accumulation of fluid in the pleural space. It is a relatively common finding in clinical practice. The diagnostic approach to the patient presenting with a pleural effusion is aimed at defining the effusion as a transudate or an exudate. This review summarises the initial assessment and investigation of pleural effusions diagnosed during the acute medical take, and who should be referred for specialist advice. In addition, recent developments, including the measurement of NT-proBNP levels and diagnostic markers for mesothelioma, are presented.

Keywords

Pleural effusion, diagnosis.

Introduction

A pleural effusion is the accumulation of fluid in the pleural space. It is a relatively common finding in clinical practice. One Czech study found an incidence of 3.2 per 1000 population per year, including effusions diagnosed at autopsy.¹ However, twenty years have elapsed since these data were collected making extrapolation to the UK difficult.

The volume of pleural fluid found in a healthy individual is around 4–13ml per hemithorax.² Abnormal volumes of fluid accumulate through the following mechanisms: increased permeability of pleural, increased pulmonary capillary pressure, decreased negative intrapleural pressure, decreased oncotic pressure, and obstruction to lymphatic flow.³

The initial diagnostic approach to the patient presenting with a pleural effusion is aimed at defining the effusion as a transudate or an exudate. The British Thoracic Society (BTS) have published guidelines on pleural effusion investigation,³ although due to a lack of an evidence base, these are largely drawn from

expert opinion and observational studies. The BTS algorithm for the approach to investigating a pleural effusion is shown in Figure 1. The causes of pleural effusion are listed in Table 1.

Clinical Evaluation: Symptoms and Signs History

Patients may present with dyspnoea, cough and/or pleuritic chest pain. These are non-specific symptoms, although dyspnoea out of proportion to effusion size in the context of pleuritic pain should raise the suspicion of pulmonary embolism.⁴ Taking a thorough clinical history may identify the presence of underlying disease responsible for the effusion, e.g. heart failure, cirrhosis or connective tissue disease. A recent history of trauma should raise the possibility of haemothorax or chylothorax. Recent cardiothoracic or abdominal surgery can cause pleural effusions; coronary artery bypass graft surgery is the 6th most common cause of pleural effusion in the USA.⁵ The drug history may highlight certain medications which have been implicated in the development of exudative pleural effusions. Those with over 100 globally reported cases of effusion include phenytoin, can be from the Pneumotox website methotrexate, amiodarone and nitrofurantoin.³ Comprehensive list of implicated medications.⁶ The occupational history may reveal previous exposure to asbestos, thus increasing the likelihood of mesothelioma and benign asbestos-related pleural effusion. In addition, a history of heavy smoking may prompt consideration of malignancy.

Examination

Clinical examination typically reveals reduced tactile fremitus, a stony dull percussion note, and absent or reduced breath sounds on the affected side. In the

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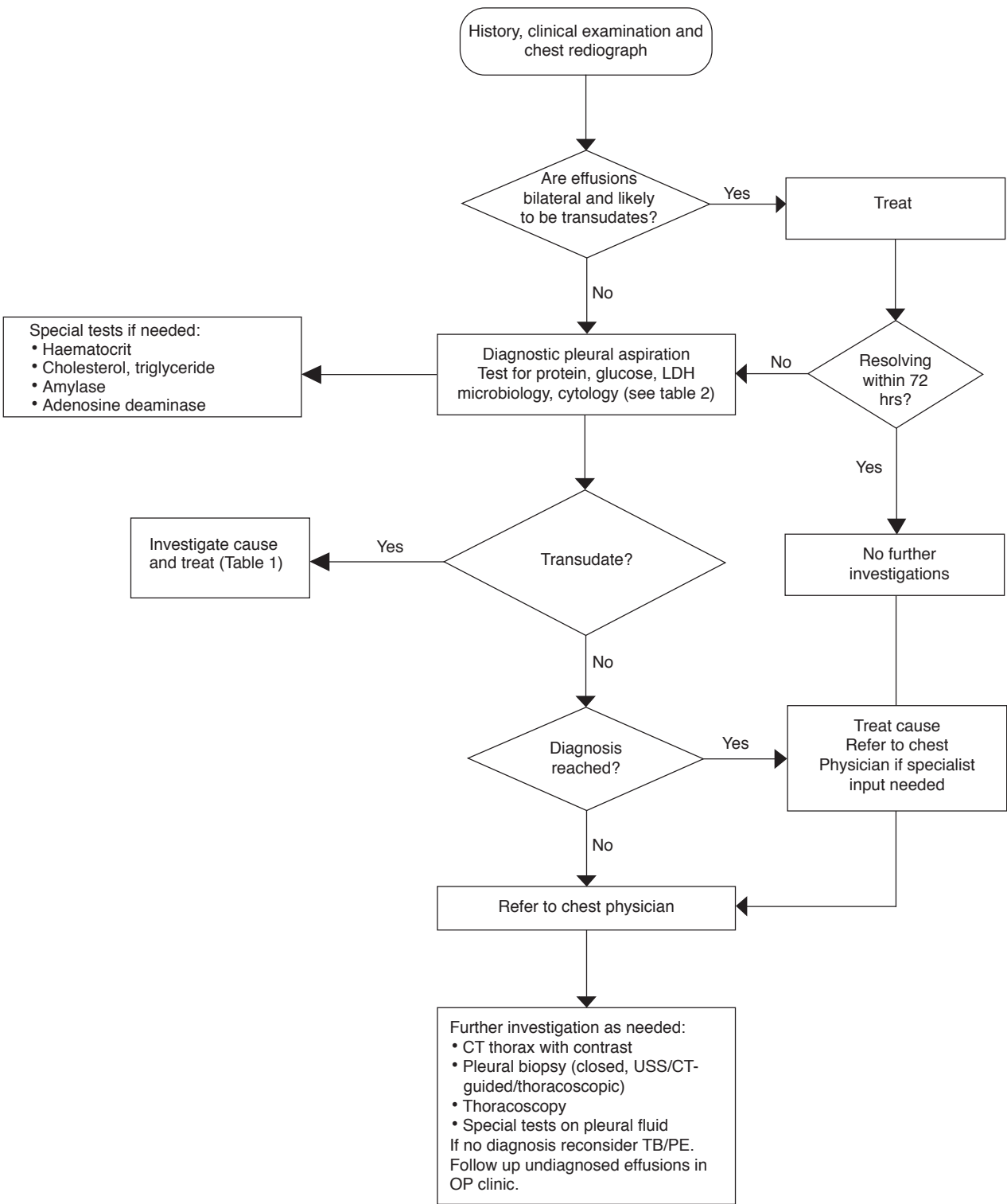


Figure 1. Algorithm for the diagnostic approach to pleural effusions. Adapted from Maskell *et al.*¹ with permission. CT: computed tomograph, USS: ultrasound scan, PE: pulmonary embolism, TB: tuberculosis, OP: outpatient, LDH: lactate dehydrogenase.

case of massive effusion, the trachea may be deviated away from the affected side. The aetiology of the effusion may be indicated by other findings on examination:

- CCF: elevated JVP, gallop rhythm and peripheral oedema;
- Cirrhosis: signs of chronic liver disease;

- Cancer: cachexia, hepatomegaly, lymphadenopathy;
- PE: pleural rub, prominent P₂ heart sound, clinical evidence of deep venous thrombosis.

When the clinical picture suggests one of the common causes of transudative pleural effusion, such as cardiac failure or cirrhosis, and the effusions are bilateral, thoracentesis

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	Transudate	Exudate
Common Causes	Cardiac failure Cirrhosis Hypoalbuminaemia Peritoneal dialysis	Parapneumonic Malignancy
Less Common Causes	Hypothyroidism Nephrotic syndrome Pulmonary embolism	Pulmonary infarction Post cardiac injury syndrome Rheumatoid arthritis Connective tissue diseases Benign asbestos effusion
Rare Causes	Urinothorax Superior vena cava obstruction Ovarian hyperstimulation Meigs' syndrome	Drugs Yellow nail syndrome Fungal infections

Table 1. Causes of pleural effusions. Adapted from Maskell *et al.*³ with permission.

is only recommended if the effusions do not respond to treatment of the underlying condition.³ In the presence of atypical symptoms, such as chest pain or fever, diagnostic aspiration should be undertaken.⁵

Diagnostic Imaging

Chest Radiography

A minimum of 200 ml of fluid in the pleural space is required before blunting of the costophrenic angle is seen on a plain PA chest radiograph. As little as 50 ml of fluid can be detected on an erect lateral film.⁷ When patients are imaged in a supine position, such as in the intensive care unit, effusions do not have their characteristic appearance and can be difficult to detect. A hazy appearance is often seen over the affected hemithorax although vascular shadows are preserved.³ Ultrasound confirmation is often required before diagnostic pleural aspiration. Similarly, subpulmonic effusions are difficult to detect with plain radiography, the only sign often being an apparently raised hemidiaphragm.³ Ultrasonography or a lateral decubitus film can confirm the diagnosis.

Massive pleural effusion involving the entire hemithorax can cause mediastinal shift away from the affected side. When mediastinal shift is not present, collapse of the underlying lung and a possible bronchial obstructing lesion should be considered.⁸ The presence of a massive or large effusion may narrow the differential diagnosis (Figure 2). One study found that 50% of such effusions were due to malignancy.⁹ Tuberculous and parapneumonic effusions accounted for a further third of the remainder. Fewer than 5% were found to be transudates. In developing countries, tuberculosis would account for a larger proportion of massive effusions due to the higher prevalence of the disease (Figure 3).

Ultrasonography

Chest ultrasound is increasingly used to aid in diagnosis and investigation of effusions. Physicians in the Accident and Emergency Department are frequently trained in its use in trauma patients, and an increasing number of acute physicians are employing ultrasound in their daily

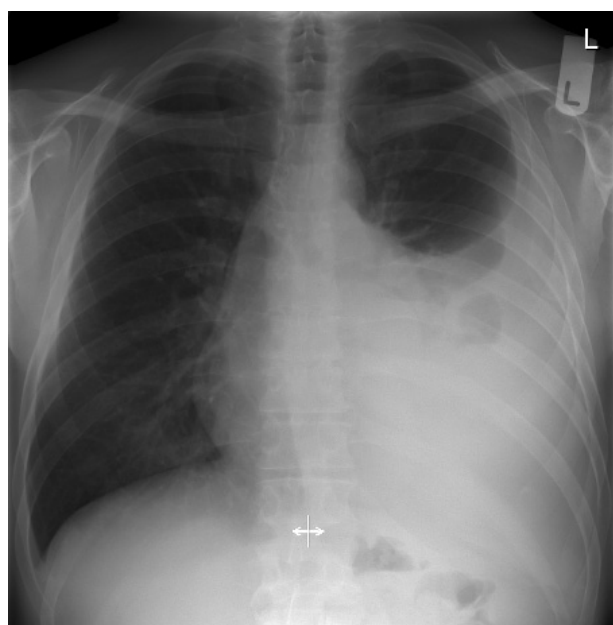


Figure 2. Large left-sided pleural effusion. A large pleural effusion occupies > two-thirds of the pleural cavity without obliterating it. Pleural aspiration revealed a blood-stained exudative effusion. Cytological analysis confirmed a malignant effusion from a primary renal cell carcinoma.

practice. Its portability makes it ideal for use for bedside imaging in these settings and the Medical Admissions Unit. Ultrasonography is more accurate than plain radiography in diagnosing effusions,¹⁰ particularly in the supine patient, and is more accurate than CT in diagnosing septated effusions (Figure 4).³ It is frequently used in the clinical setting following unsuccessful 'blind' aspiration, or if an effusion is felt to be too small on chest radiograph to safely aspirate.

Computed Tomography (CT)

CT scan of the chest is usually requested by a chest physician when pleural fluid analysis has not been diagnostic (see Figure 1). The BTS recommend that CT scans should be contrast-enhanced, and should ideally

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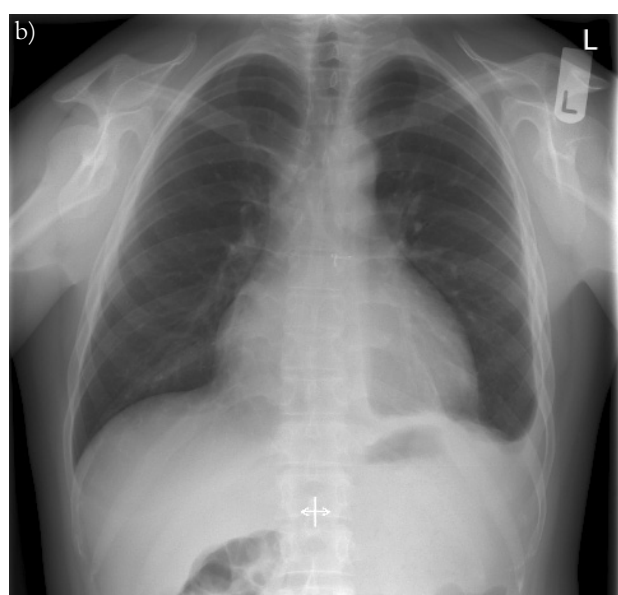
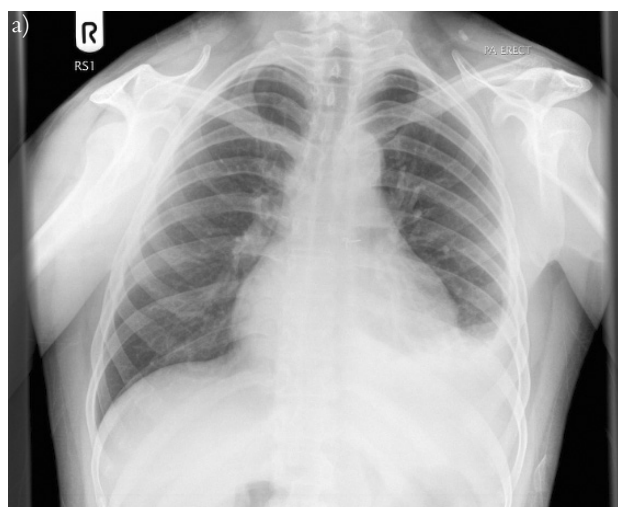


Figure 3. (a) Tuberculous pleural effusion. This patient originated from a high-prevalence area. Mycobacterial culture of the fluid unusually confirmed the diagnosis of tuberculosis. The radiograph in (b) shows significant improvement of the effusion following 3 months of anti-tuberculous therapy.

be undertaken before pleural fluid has been completely drained.³ This improves imaging of the pleura and will make pleural biopsy easier if this is subsequently needed. CT helps to distinguish malignant from non-malignant pleural disease,¹¹ parenchymal from pleural disease, and can aid in the assessment of loculated pleural effusions.³ CT pulmonary angiography is also the imaging modality of choice when investigating pleural effusion due to suspected pulmonary embolism.

Diagnostic Pleural Aspiration

This is indicated in all patients with pleural effusion other than those with suspected bilateral transudative effusions.³ 80% of effusions due to cardiac failure will be bilateral, of which 75% would be expected to resolve with 48 hours of diuretic therapy.¹² Therefore, an effusion which is unilateral, or one that persists after 72 hours of diuretic



Figure 4. Ultrasound image of septated pleural effusion. Pleural aspiration yielded frank pus indicating empyema.

treatment should be aspirated.⁵ The BTS recommends that a 21 gauge needle and 50ml syringe are adequate to perform pleural aspiration.³ If the effusion appears small on chest radiograph, or if clinical examination does not clearly demarcate the upper border of the effusion, ultrasound-guided aspiration is recommended. By entering the thoracic cavity as close as possible to the superior border of the lower rib, accidental puncture of the intercostal artery is minimised.

The sample should be divided into three sterile specimen bottles for cytology, microbiology and biochemistry. A few millilitres of fluid can also be aspirated into a heparinised arterial blood gas syringe for measurement of pH. Frank pus may clog the blood gas analyser and should therefore not be sent for pH analysis.⁸ Inoculation of pleural fluid in to blood culture bottles improves the diagnostic yield of cultured organisms.¹³ The routine tests requested for pleural fluid analysis are summarised in Table 2.

Pleural Fluid Analysis

Bedside Observation

The colour of pleural fluid should be documented in the medical notes as one of the following: serous, blood-stained, or frankly bloody. In addition, turbidity or frank purulence should be noted. Aspiration of pus indicates the presence of empyema. If this smells putrid, anaerobic organisms are likely to be responsible for the empyema.³

Less common appearances of pleural fluid can be diagnostic of rarer conditions:³

- *milky*—chylothorax, pseudochylothorax
- *presence of food particles*—oesophageal rupture (usually left sided)
- *bile stained*—cholothorax (biliary fistula)
- *'anchovy sauce'*—ruptured amoebic abscess
- *urine colour and smell*—urinothorax

If the effusion is blood-stained, haematocrit estimation helps in the diagnostic process.³ A haematocrit >50% of that in a paired sample of whole blood is diagnostic of haemothorax. A haematocrit <1% is not significant. If the haematocrit is between these two values, the differential diagnosis includes: malignancy, pulmonary embolism, trauma, benign asbestos pleural effusion, and post-cardiac injury syndrome.¹⁴

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Destination	Specimen Container	Tests
Biochemistry	Sterile container Arterial blood gas syringe	LDH, protein, glucose pH
Microbiology	Sterile container	Microscopy for gram stain and bacterial culture; Mycobacterial stain and culture.
Pathology	Sterile container	Cytology

Table 2. Pleural fluid aspiration: specimens required for routine testing.

Distinguishing Exudates from Transudates

Traditional teaching has used a pleural fluid protein concentration of 30 g/l as the cut off between transudate (<30 g/l) and exudate (>30 g/l) when the serum protein concentration is within normal limits. However, when pleural fluid protein lies between 25 and 35 g/l, the diagnostic ability of the test is compromised. In this situation, serum and pleural fluid LDH should be measured to allow Light's criteria to be used (Table 3). If one or more of the three criteria are met, the effusion can be called an exudate with 98% sensitivity and 83% specificity.⁵ These criteria, originally reported in 1972,¹⁵ remain the best performing diagnostic test to distinguish between exudates and transudates.⁵ However, Light's criteria misclassify around 20% of patients with transudative effusions treated

Test	Criteria
Pleural fluid protein: serum protein ratio	>0.5
Pleural fluid LDH: serum LDH ratio	>0.6
Pleural fluid LDH	>two-thirds the upper limit of the normal range for serum LDH

Table 3. Light's criteria to differentiate an exudative effusion from a transudate.¹⁵ If one or more of the criteria are met, the effusion is an exudate.

with diuretics as exudates.³ In this situation, a further test, the difference between serum and pleural fluid albumin should be undertaken. A value >12 g/l indicates that the effusion is a transudate.¹⁶

Routine Pleural Fluid Tests

Glucose

Exudative effusions with a glucose <3.3 mmol/l include: empyema, rheumatoid arthritis, systemic lupus erythematosus, tuberculosis, malignancy and oesophageal rupture.³ A low glucose is usually associated with a low pH and high LDH. Empyema and rheumatoid arthritis tend to have very low glucose levels (<1.6 mmol/l).

pH

Normal pleural fluid has a pH of 7.6 due to an accumulation of bicarbonate. The causes of a low pH are the same as those causing a low glucose. Where malignant pleural effusion is confirmed, a pH <7.3 is associated with more extensive

disease and a reduced survival.¹⁷ A pH of <7.2 in the context of pleural infection indicates the need for drainage of the pleural cavity with an intercostal drain.³ In addition, aspiration of frank pus or identification of organisms on a gram stain necessitate drain insertion.¹⁸ Further information relating to the specific management of pleural infection and malignant pleural effusions can be found in comprehensive guidelines published by the BTS.^{18,19}

Ancillary Pleural Fluid Tests

Amylase

Amylase levels should be measured when pancreatitis or oesophageal rupture is suspected.³ An elevated pleural fluid amylase level is indicated by an absolute value higher than the upper limit of the normal serum reference range, or a pleural fluid:serum ratio >1.0.³ Pleural fluid amylase is also raised in ruptured ectopic pregnancy or malignancy (around 10%).

Cholesterol and Triglycerides

If pleural aspiration yields milky fluid or if a chylothorax is suspected, pleural fluid cholesterol and triglyceride levels should be measured. A chylothorax is caused by the accumulation of lymph in the pleural space due to disruption of flow in the thoracic duct. It is usually caused by malignancy (lymphoma or metastatic cancer) but also complicates thoracic surgery or trauma.³ A pseudochylothorax is the result of cholesterol crystal formation in a chronic pleural effusion, usually due to rheumatoid pleurisy in the UK. The two conditions are distinguished by the following criteria:

- chylothorax
 - triglycerides >1.24 mmol/l
 - cholesterol <5.18 mmol/l
 - chylomicrons present
- pseudochylothorax
 - triglycerides <0.56 mmol/l
 - cholesterol >5.18 mmol/l
 - cholesterol crystals present

Tests for Tuberculosis

Pleural fluid culture for tuberculosis is positive in 20–40% of cases, which improves when combined with pleural biopsy histology and culture to 80–90%.²⁰ Adenosine deaminase (ADA) is found in all cells, but has a particular role in immune cell proliferation and activation.²¹ It is elevated

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in exudative effusions of many causes, but is particularly elevated in tuberculous exudates. It has a sensitivity of 90% in a recent meta-analysis.²¹ However, due to the low prevalence of tuberculosis in the UK, the positive predictive value of the test is low. Alternative diagnostic assays for tuberculosis include interferon- γ and PCR which have a similar sensitivity and specificity to ADA.²²

Recent Developments

NT-ProBNP

B-type (formerly brain) natriuretic peptide (BNP) is produced by cardiac myocytes in response to stretching in heart failure. BNP is derived from a pro-hormone, proBNP, which is cleaved into the active hormone, BNP, and the inactive amino-terminal fragment, NT-proBNP on an equimolar basis. NT-proBNP is more biologically stable and therefore easier to measure in serum samples.²³ A cut off value of between 1500 and 4000 ng/l has >90% sensitivity and specificity for the diagnosis of pleural effusion due to heart failure in pleural fluid.^{24,25} Although serum and pleural fluid concentrations of NT-proBNP correlate well,²⁴ the diagnostic benefit of pleural fluid analysis over serum measurement is yet to be determined.

Mesothelin

Mesothelioma, an asbestos-related malignancy of the pleura, is difficult to diagnose from cytological analysis of pleural fluid.²⁶ Soluble mesothelin, which can be measured in the pleural fluid of patients with the disease, has the potential

to be used as a diagnostic marker for mesothelioma. In a recent study, a pleural fluid mesothelin level greater than 20 nM had a diagnostic specificity of 98% and sensitivity of 67%.²⁷ False positives were found in cases of other malignancies: lung, pancreatic, ovarian, and lymphoma.

Pneumococcal Antigen

Urinary pneumococcal antigen is frequently measured in patients presenting with community acquired pneumonia. A recent study has shown measurement of this antigen in pleural fluid has a sensitivity of 71% and specificity of 93%.²⁸ It is not clear if this adds to the diagnostic information obtained from urinary antigen measurement. The latter has a diagnostic sensitivity of 82% and does not require an invasive procedure to obtain a specimen. Further clinical studies will be required before pneumococcal antigen is measured routinely in pleural fluid specimens.

When to Refer to a Respiratory Physician

Parapneumonic effusions requiring tube drainage and empyemas will require respiratory specialist involvement.¹⁸ In addition, if initial investigations have failed to find the cause of a pleural effusion, referral to a chest physician is recommended.³ At this stage, a CT scan may be requested if underlying malignancy is suspected. The respiratory physician may undertake a closed pleural biopsy, or refer for a thorascopic or ultrasound/CT-guided biopsy.

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