THE MODERN DIAGNOSIS AND MANAGEMENT OF PLEURAL EFFUSIONS

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This review was jointly conceived and written by both RB and NM, with NM acting as guarantor. Both authors have approved the manuscript and all associated figures.

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Introduction

A pleural effusion describes an excess of fluid in the pleural cavity and usually results from an imbalance in the normal rate of pleural fluid production, absorption, or both. Pleural effusions are a common problem with an estimated 1 - 1.5 million new cases in the United States and 200 - 250,000 in the United Kingdom each year. [1] This review describes, with a particular focus on the emerging phenomenon of ambulatory management, how pleural effusions may be investigated and treated in both the community and in secondary care.

Sources and selection criteria

We searched the PubMed, Embase, and Medline databases as well as the Cochrane database of systematic reviews. The primary search terms included “pleural effusion” and “indwelling pleural catheter” with only abstracts published in English relating to adults being included. Priority was given to randomised controlled trials and meta-analyses although citations from case series and retrospective studies have also been included where appropriate. Further information was obtained from our personal libraries, trial registration databases (such as www.isrctn.com) and from conference proceedings where necessary.

Main text

What are the most common causes of pleural effusions?

There are over fifty recognised causes for pleural effusions, [2] spanning a wide variety of medical specialties. The aetiology is often classified initially as either a transudative or exudative process, with the former usually associated with cardiac, renal or hepatic dysfunction and the latter with conditions which cause an excess of inflammation such as malignancy or infection. The commonest

cause of a transudate, and probably effusions as a whole, is heart failure. [1] Cross-sectional data from an elderly UK general practice population indicates that the prevalence of effusions in association with left ventricular may be as high as 500,000. [3]

An exudate is most likely to be associated with pneumonia. Estimates suggest that up to 57% of such patients will develop pleural fluid, [4] although not all of these will require intervention. [5] Of the other conditions which may lead to an exudate, malignancy is the most important in terms of further investigations and long-term outcome. [6] The American Thoracic Society guidelines on the management of MPE, published in 2000, estimated the incidence in the United States to be between approximately 80,000 and 160,000 new cases per year. [7]

What are the important points to address in the patient history and when should patients be referred?

The way in which a pleural effusion presents depends on a number of factors such as effusion size; rate of fluid accumulation; comorbidities; and underlying respiratory reserve. The history should be focused on determining the severity and rate of onset of symptoms, and thus the need for intervention; and an exploration of any potential causes. Effusions which develop rapidly (over hours to days rather than weeks to months) are likely to be due to a limited number of causes, examples of which include chest wall injury or recent chest infection (parapneumonic). Collections which appear more slowly raise the suspicion of more chronic processes, with the presence of constitutional symptoms potentially pointing towards empyema, malignancy or tuberculous pleuritis. **Box 1** details other important points to address when eliciting a history from a patient with an effusion, with **Box 2** describing the likely clinical symptoms and signs.

When and who to refer to secondary care with a suspected pleural effusion will be subject to a degree of geographical variation. In general however, virtually all cases of unexplained unilateral

effusion; non-resolving bilateral effusions; or effusions due to suspected chronic infection, malignancy or haemothorax should at the very least be discussed with secondary care providers, as these cases are much more likely to require more aggressive investigation or definitive management. A patient's use of any anticoagulant or antiplatelet medications should be made clear at the time of referral as this may require stopping on a temporary basis to facilitate investigations.

How should suspected pleural effusions be investigated in primary care?

Chest imaging

In general, the simplest and most widely available test to investigate a suspected pleural effusion is the chest radiograph. Although the presence of even small collections may be suggested by changes on erect chest X-ray, moderate to large effusions are usually more recognisable as dense opacification which forms the outline of a meniscus superiorly. Very large effusions may lead to the classical 'white-out' of the affected hemithorax. **(See figure 1)** In patients with this radiographic appearance but in whom recent imaging suggests little fluid, or in whom there is a very rapid deterioration in symptoms, lobar collapse should be considered as an alternative diagnosis.

Computed tomography (CT) scans have now become a standard part of the diagnostic work-up of a new effusion. They are undertaken with a view to providing greater diagnostic information and may be able to reveal a likely cause (such as a primary tumour) or potential biopsy site if pleural thickening or nodularity is seen. [8] CT may also be used to better characterise the size and location of separate pockets ('locules') of fluid, which may in turn guide later interventions.

Other tests

Standard blood tests for the investigation of an effusion should include a full blood count, looking for evidence of infection or platelet abnormality, and liver and renal function to investigate for

transudative causes including hypoalbuminaemia. In those with bilateral effusions tests such as a transthoracic echocardiogram or serum NT-pro brain natriuretic peptide (NT-proBNP) may be of benefit in identifying or ruling out cardiac failure as contributory. [9]

The increasing importance of ambulatory care

Traditionally, the majority of patients who were found to have a pleural effusion would be admitted to hospital for drainage and further investigations. This approach, which often entails inpatient stays of many days, is now seen by some as unnecessary. Changes to both attitudes and technology have meant that outpatient investigation and management of patients with pleural effusions is increasingly common, and this has been further facilitated by the creation of dedicated pleural teams, clinics and procedure lists in many institutions. These have the potential to both improve a patient's overall experience and lead to significant cost savings for healthcare providers. [10]

Primary care and acute practitioners play a vital role in the success of ambulatory pleural management. Patients who have confirmed or suspected collections which are not causing significant respiratory distress may avoid an emergency admission altogether if an urgent outpatient appointment with a pleural team can be arranged in its stead. Those patients who are admitted may be able to be discharged more rapidly following a large-volume ('therapeutic') pleural aspiration (of typically 1000 – 1500mls), which aims to simply relieve symptoms transiently (and begin fluid diagnostics) prior to an urgent outpatient follow-up visit, at which further investigations and definitive management can be arranged.

How might pleural effusions be investigated in secondary care?

Fluid sampling

A diagnostic ‘tap’ is a routine first invasive step in the investigation of a pleural effusion and can be carried out simply in many settings, including outpatients. Samples are routinely analysed for protein, glucose, and lactate dehydrogenase with a view to establishing features, using Light’s criteria, [11] of either a transudate or exudate. Fluid pH can also be rapidly assessed in non-purulent samples to aid decision making regarding the need for urgent chest tube drainage (for example, a pH value <7.20 in cases of likely parapneumonic effusion).

It is now considered best practice that such aspirations (as well as any later, more invasive procedures such as drain insertion) are carried out under thoracic ultrasound guidance. This technique has been increasingly adopted by respiratory physicians and has been shown, in both well-conducted randomised studies and very large-scale retrospective series, to improve both the utility and safety of pleural intervention. [12 13]

Other routine tests on fluid will usually include cytological examination and microbiological culture. Cytological examination can help to determine whether a pleural biopsy procedure is required. In cases of malignancy sensitivity rarely exceeds 60%, [14] however, a positive result may help to avoid more invasive testing altogether.

Pleural biopsy

Many pleural services can now offer a variety of methods to obtain pleural tissue without the need for a lengthy hospital admission or a surgical biopsy requiring general anaesthetic (although this approach still remains the gold standard for a subset of patients). CT-guided pleural biopsy can be performed as a day-case and has been shown to be almost twice as effective as blind (Abram’s) biopsy for the detection of malignancy in one randomised study, with a pick-up rate of 87%. [15]

An alternative to radiological biopsy is local anaesthetic (‘medical’) thoracoscopy (LAT) performed under light sedation. This technique is usually performed by respiratory physicians and is

increasingly available to many centres, its main benefit being that it generally allows for the diagnosis and management of an effusion as part of the same procedure. LAT has been shown to offer malignant diagnostic yields as high as those seen with the more invasive surgical techniques [16] and in some cases can be performed as a day-case procedure.

A flow chart for the initial investigation of a pleural effusion can be found in **figure 2**.

How can recurrent pleural effusions be managed?

Control of breathlessness

For the majority of patients, the best approach will be the removal of pleural fluid. However in some, alternative methods of symptom control which avoid intervention may be more appropriate. Such patients should be treated as for chronic breathlessness with opiate-based medication such as oral morphine, which can have significant benefits on dyspnoea, [17] or benzodiazepines if secondary anxiety is the primary symptom. [18] The optimisation of medical therapies for underlying medical conditions, especially those which might be driving effusions, is also important. Unless severely hypoxemic, oxygen therapy is usually not recommended. [19]

Recurrent aspirations

The decision regarding how to manage a recurrent pleural effusion should be made on a case-by-case basis as not all available treatments are suitable (or desirable) for all patients. The least invasive approach is repeated therapeutic aspiration. This is usually reserved for those at the end of life or for those in whom more substantial procedures would pose too high a risk. [20] This method may also be advocated if the frequency of fluid recurrence is particularly low.

Pleurodesis

Pleurodesis involves the obliteration of the pleural space through the rapid stimulation of inflammation and fibrosis between the visceral and parietal membranes. For this to be successful,

the chest must first be emptied of fluid using either a standard intercostal drain insertion or a thoracoscopic technique, and there must also be evidence that the lung is able to expand fully (is not 'trapped'). A chemical irritant is then inserted through the drain or applied at the end of the thoracoscopy, with patients typically requiring up to week in hospital in total. [21] Cochrane meta-analysis data would suggest that the most effective pleurodesis agent is sterile talc powder [22] and this has now been adopted as standard in many parts of the world. Although there remains debate as to the most effective method for delivery of talc, quoted success rates are usually around 80% at one month post-procedure. [20]

Indwelling pleural catheters

Probably the most dramatic change in the last 20 years in the way recurrent pleural effusions are managed came with the introduction of the indwelling pleural catheter (IPC). These tunnelled chest tubes are now being increasingly used and are likely to be encountered by medical practitioners across a wide range of specialties, including in the community. IPCs can be inserted under local anaesthetic as a day-case procedure, after which fluid is drawn off periodically (usually two or three times per week) using a detachable vacuum bottle system. Drainages can be performed in only a few minutes in the patient's home by community nurses, family members, or even the patient themselves, and when not being used the IPC remains concealed under a compact dressing. **(See figure 3)**

Although there is increasing evidence that IPCs can be used for recurrent effusions of varying aetiology, [23] they are typically inserted for cases of MPE, either due to trapped lung, failed talc pleurodesis, or, increasingly, as primary therapy. The shift towards using them in this latter circumstance came as a result of the recently published TIME-2 trial, [24] which randomised 106 patients with MPE to receive either a standard talc pleurodesis or an IPC and showed there was no significant difference between the two arms in the primary endpoint of patient-reported dyspnoea at six weeks.

Further to this, large, retrospective, international series have shown that IPCs are both safe and effective for the long-term control of effusions, with low rates of pleural infection and hospital re-admission once sited. [25 26] Smaller-scale studies have also suggested that they are cost-effective [27] (despite the on-going use of consumables) and may be used safely in those patients undergoing chemotherapy. [28]

What does the future hold for managing pleural effusions?

Although there has traditionally been a dearth of high quality evidence relating to pleural medicine, there are an increasing number of on-going, well-conducted studies. The future of pleural effusion management is likely to become progressively more patient-centred and personalised, as exemplified by the recent publication of the first validated prognostic scoring system for patients with proven MPE. [6] Therapies combining various strategies, such as IPC placement at the time of thoracoscopy or talc slurry pleurodesis via an IPC, [29 30] have recently been advocated as potentially beneficial approaches, although randomised studies are needed. Further to these, technological creativity has seen the development of novel drainage devices, including drug-eluting IPCs and pleuro-vesical automated pumps, both of which have been tested successfully in animal models. [31 32]

BOX 1 – Important history points for patients with suspected or confirmed effusions

- Severity, duration and rate of onset of breathlessness, cough or chest pain
- Presence of constitutional symptoms such as fevers, sweats or weight loss
- Recent injury or interventions to chest
- Recent illnesses, especially related to chest
- Recent hospital admissions or operations, especially cardiac surgery
- History of malignancy, or current active malignancy
- Previous exposure to tuberculosis
- Full occupational history, with names and dates of employers if known*
- Asbestos (or asbestos-like substance) exposure, with clear relation to occupation and description of level of exposure (e.g. did the patient work with it directly?)*
- Tobacco smoking history
- Medications, including recent changes to prescriptions and the use of any anticoagulants
- Assessment of evidence of uncontrolled cardiac, hepatic or renal failure

** These questions may be more easily and fully explored in the secondary care setting*

BOX 2 – Symptom and clinical signs associated with a pleural effusion

- Symptoms
    - Dyspnoea
    - Cough, usually dry
    - Chest pain, usually pleuritic
- Signs
    - 'Stony' dullness to percussion over the affected portion of the hemithorax
    - Reduced chest expansion on the affected side (if moderate to large)
    - Reduced breath sounds on auscultation, occasionally with an area of bronchial breathing above the effusion

BOX 3 – Indwelling pleural catheter management tips

- Monitor insertion site and subcutaneous track for infection
- Changes in fluid colour may be normal, but discuss with secondary care if concerned
- Air may be withdrawn if there is trapped lung
- Patients can shower and bathe with an IPC, but drains and dressings should not remain wet for extended periods
- If the one-way valve is damaged or becomes unattached then clamp the tube and discuss with secondary care
- An IPC can be attached to a normal underwater seal (using the correct adaptor) if continuous drainage is needed. Remember that IPCs are not usually sutured to the skin so ensure adequate adhesive dressings are used if accessed for long periods
- Pleural infection associated with an IPC can usually be managed without removal of the tube
- IPCs are not a contraindication to chemotherapy

BOX 4 – Tips for the non-specialist

- Consider the diagnosis of a pleural effusion in all patients with breathlessness and the appropriate clinical signs
- Confirm suspicions with further imaging – chest radiograph will be the usual first line test
- Ask about, and clearly document, asbestos exposure history
- Inform secondary care of any anticoagulant or antiplatelet use at the time of referral or before any procedure – warfarin or newer anticoagulants are contraindications to pleural intervention and will need to be stopped.
- Patients admitted acutely with moderate to large effusions may become suitable for outpatient management following a therapeutic thoracentesis
- All pleural procedures for fluid should be performed under ultrasound guidance

BOX 5 – Ongoing research

- There is a dearth of high-quality epidemiological data relating to pleural effusions in general. The international multicentre Pleural Infection Longitudinal Outcome Trial (PILOT) is currently looking to address one aspect of this by collecting data relating to the management of patients with pleural infection. (ISRCTN50236700)
- Much of the evidence relating to the management of malignant pleural effusion is based on small or non-randomised studies. The 2004 Cochrane meta-analysis in this area is currently being updated and will hopefully be available within the next 6 months.
- The ideal way to undertake talc pleurodesis remains unclear. The TAPPS trial is a UK multicentre randomised controlled study currently in active recruitment which compares talc slurry to talc poudrage for patients with malignant pleural effusions. (ISRCTN47845793)
- Ambulatory talc pleurodesis may dramatically alter how patients with MPE are managed. The IPC-Plus trial is a UK multicentre randomised controlled study comparing the use of IPC alone with IPC in combination with talc slurry, with completion expected in the next 12 months. (ISRCTN73255764)
- The role of IPCs in the treatment of non-malignant effusions is also under-researched. The REDUCE study, which has recently opened in the UK, randomises patients with hepatic or cardiac disease-related effusions to receive either recurrent aspirations or an IPC. (UKCRN ID 17127)

BOX 6 – Additional educational resources

- British Thoracic Society Pleural Disease Guideline 2010
- Efficacy and Safety of Tunneled Pleural Catheters in Adults with Malignant Pleural Effusions: A Systematic Review [25]
- Developing a 'pleural team' to run a reactive pleural service [33]

BOX 7 – Information for patients

- British Lung Foundation – Mesothelioma information (http://www.blf.org.uk/Page/Mesothelioma)
- MacMillan Cancer Support – Pleural effusion information (http://www.macmillan.org.uk/information-and-support/coping/side-effects-and-symptoms/other-side-effects/pleural-effusion.html)

Box 8 – The bottom line

- Pleural effusions are common and may be caused by a variety of underlying illnesses
- An undiagnosed unilateral pleural effusion, without a history suggestive of acute infection, should be considered malignant until proven otherwise
- Bilateral effusions are usually due to cardiac, renal or hepatic impairment – treatment of the cause will usually improve effusions without the need for intervention
- Chest x-ray and CT are vital early tests in the diagnosis of pleural effusions
- There is an increasing drive to diagnose and manage effusions in the outpatient setting, with pleural clinics and medical thoracoscopy streamlining the diagnostic pathway
- Indwelling pleural catheters can now allow many patients with recurrent effusions to be managed at home

Box 9 – A patient's perspective from Mr Ronald Huish

Swimming and some gentle exercise in the gym was my way of keeping reasonably fit, until the latter part of 2012. Then the end of swimming pool seemed further away each length and recovering breath became more and more difficult. My G.P. sent me for a chest x-ray and echocardiogram, assuming it was caused by the heart, but these tests in fact showed that there was a large build-up of fluid around the left lung. I was referred urgently to my local hospital's pleural team and underwent a number of investigations including blood tests, a CT scan, ultrasound scans, and a thoracoscopy. Although no diagnosis was made initially (I was later found to have amyloidosis) I appreciated being kept fully informed at every stage, and that the team always made it a priority to keep the number of days I spent in hospital to a minimum – in fact, during all of my investigations I only spent two nights as an inpatient. Because the fluid kept returning I had outpatient drainages on a number of occasions and ultimately the decision was made in April 2013 to fit an IPC. It took a few days to feel the full benefits with regular draining but there is no doubt it solved the immediate problem of shortness of breath and has allowed me to continue a reasonable normal life style from then on, even to the extent of resuming gentle exercise in the gym. Unfortunately swimming is still not possible, but that's not the fault of the IPC! This treatment has improved my quality of life in every way and given me back a freedom beyond what I had expected when I was first told about the effusion.

Figure legends

Figure 1 – The varying appearances of a pleural effusion. A: small bilateral effusions; B: moderate left-sided effusion; C: large left-sided effusion; D: left-sided loculated pleural effusion with intercostal drain in situ. ***(Consent forms provided)***

Figure 2 – Algorithm for the early investigation of a suspected pleural effusion. CT = Computed tomography; LDH = Lactate dehydrogenase.

Figure 3 – An indwelling pleural catheter in situ, dressed (left) and undressed (right) prior to drainage ***(Consent form provided)***

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