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CLINICAL REVIEW

The modern diagnosis and management of pleural effusions

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

What are the most common causes of pleural effusions?

More than 50 causes of pleural effusions are recognised,[2] spanning a wide variety of medical specialties. The cause is often classified initially as either a transudative or an exudative process, with the former usually associated with cardiac, renal, or hepatic dysfunction and the latter with conditions that cause an excess of inflammation, such as malignancy or infection. The most common cause of a transudate, and probably effusions as a whole, is heart failure.[1]

An exudate is most likely to be associated with pneumonia. Estimates suggest that up to 57% of patients with pneumonia will develop pleural fluid,[3] although not all will require intervention.[4] Of the other conditions that may lead to an exudate, malignancy is the most important in terms of further investigations and long term outcome.[5] The American Thoracic Society guidelines on the management of malignant pleural effusion, published in 2000, estimated the incidence in the US to be between 80 000 and 160 000 new cases each year.[6]

Despite the seemingly clear distinction between exudates and transudates, the clinical reality of determining the cause of a pleural effusion is often much more nuanced. Patients may present at different times along their disease course, with varying symptoms, and their condition may even have more than one contributory factor. Careful consideration of the whole patient story is vital to ensure timely and appropriate management.

What might be relevant in the history and when should patients be referred?

How a pleural effusion presents depends on several factors such as the size of the effusion, the rate of fluid accumulation, comorbidities, and underlying respiratory reserve. Patients routinely mention at least one of dyspnoea, cough (non-productive), or chest pain (usually pleuritic). The initial 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 that develop rapidly (over hours to days rather than weeks to months) are likely to result from a limited number of causes, examples of which include injury to the chest wall or recent chest infection (parapneumonic). Collections that 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. Clinically, findings typically include "stony" dullness to percussion and reduced chest expansion on the affected side of the hemithorax, as well as reduced breath sounds on auscultation over the effusion. An area of bronchial breathing may also be present in the region superior to the fluid.

When and who to refer 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 least be discussed with secondary care providers, as these cases are likely to require more aggressive investigation or definitive management. At the time of referral a patient's use of any anticoagulant or antiplatelet drug should be established as this may need to be stopped on a temporary basis to facilitate investigations.

Those receiving referrals will also vary from location to location. Any service with the facility to perform the secondary care investigations and follow-up, including "acute" clinicians and

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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 proved 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 radiography and computed tomography are vital early investigations in the diagnosis of pleural effusions
- Both the safety and the success of pleural procedures are improved by the use of thoracic ultrasonography to guide needle placement
- 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

Sources and selection criteria

We searched through PubMed, Embase, Medline, and the Cochrane database of systematic reviews from inception to April 2015 using the primary search terms "pleural effusion" and "indwelling pleural catheter". We included abstracts published in English and related to adults. Priority was given to randomised controlled trials and meta-analyses, although citations from case series and retrospective studies have been included where appropriate. Further information was obtained from our personal libraries, trial registration databases (such as www.isrctn.com), and conference proceedings where necessary.

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*
- Exposure to asbestos (or asbestos-like substances), with clear relation to occupation and description of level of exposure (for example, did the patient work with a substance directly?)*
- Tobacco smoking history
- Drugs, including recent changes to prescriptions and the use of any anticoagulants
- Assessment of evidence of uncontrolled cardiac, hepatic, or renal failure

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

general respiratory doctors, should be suitable, although dedicated pleural services are increasingly becoming available.[7]

How should suspected pleural effusions be investigated in primary care?

Initial chest imaging

In general the simplest and most widely available method for the investigation of a pleural effusion is chest radiography and this should be performed initially in all patients with a newly suspected effusion—a potential exception being those who are too frail to undergo investigations. Although the presence of even small collections may be suggested by changes on erect chest radiographs, moderate to large effusions are usually more recognisable, appearing as dense opacification which forms the outline of a meniscus superiorly. Large effusions may lead to the classic "white-out" of the affected hemithorax (fig 1⇓). In patients with this radiographic appearance but recent imaging suggesting little fluid, or patients with a rapid deterioration in symptoms, lobar collapse should be considered as an alternative diagnosis.

Other tests

Standard blood tests for the investigation of an effusion include a full blood count; looking for evidence of infection, blood loss, or platelet abnormality; and liver and renal function to investigate for transudative causes, including hypoalbuminaemia. In those with bilateral effusions, in addition to the above investigations, procedures such as a transthoracic echocardiography or tests for serum NT-pro brain natriuretic peptide may be of benefit in identifying or ruling out cardiac failure as contributory, and, if performed early, may reveal a diagnosis that can be managed in primary care without the need for referral or further investigation.[8]

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, by appropriately trained staff provided imaging guidance is available. Before aspiration, patients should provide consent for the possibility of pneumothorax, pain, haemorrhage, and underlying visceral damage. The procedure is, however, generally safe, with data from meta-analysis showing that only 1.4% of procedures performed by a doctor result in a complication requiring a chest drain. This decreased to 0.9% of patients when ultrasound guidance was used to aid needle placement,[9] and indeed national guidelines now consider it best practice that aspirations (as well as any later, more invasive procedures such as drain insertion)

are carried out under thoracic ultrasound guidance. Traditionally the domain of radiologists, ultrasonography is now considered the ideal procedure for the confirmation and localisation of pleural fluid and has been increasingly adopted by respiratory doctors. In both well conducted randomised studies and large scale retrospective series, ultrasonography has been shown to improve both the utility and the safety of pleural intervention when compared with blind techniques.[10 11]

With a view to establishing a sample as either a transudate or exudate, fluid is analysed for protein and lactate dehydrogenase levels before applying Light's criteria (box 2).[12] Where pleural infection is suspected, fluid pH can also be rapidly assessed in non-purulent samples to aid decision making—a value of less than 7.20 usually being an indication for urgent chest tube drainage.

Other routine tests on fluid will usually include cytological examination and microbiological culture, with a well conducted prospective study further suggesting that inoculation of blood culture bottles with pleural fluid can increase microbiological yield by 20%.[13] 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. Box 3 describes additional tests that may be carried out in the analysis of pleural fluid.

Further imaging

Contrast enhanced computed tomography has now become a standard part of the diagnostic investigations of a new effusion and is usually performed following confirmation of a collection on chest radiography or ultrasonography and after initial sampling.[14] Scanning is typically undertaken in secondary care (although not exclusively) 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.[15] Computed tomography may also be used to characterise the size and location of separate pockets (locules) of fluid, which may in turn guide later interventions, although the identification of such locules can also be performed using thoracic ultrasonography.

Pleural biopsy

Many pleural services can now offer a variety of methods to obtain pleural tissue without lengthy hospital admission or a surgical biopsy requiring general anaesthesia (although this approach remains the ideal for a subset of patients). In one randomised study, computed tomography guided pleural biopsy was shown to be almost twice as effective as traditional blind (Abram's) biopsy for the detection of malignancy, with a detection rate of 87%, meaning blind biopsy techniques in this setting have been largely superseded in many parts of the world.[16]

Local anaesthetic ("medical") thoracoscopy performed under light sedation is an alternative to radiological biopsy. This technique is usually carried out by respiratory doctors and is becoming increasingly available in many centres, its main benefit being that it allows the diagnosis and management of an effusion as part of the same procedure. Local anaesthetic thoracoscopy has been shown to offer diagnostic yields for malignancy as high as those seen with the more invasive surgical techniques,[17] and in some cases can be performed as a day case procedure.

Figure 2⇓ presents a suggested flow chart for the initial investigation of a pleural effusion.

How important is ambulatory care?

Traditionally, most patients with a pleural effusion would be admitted to hospital for drainage and further investigations. This approach, which often entails inpatient stays of several days, is now seen by some as unnecessary. Changes to both attitudes and technology mean that the outpatient 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. Although limited at this stage, the evidence would suggest that such an approach is able to improve a patient's overall experience; one non-comparative study of an ambulatory pleural service documented that 97% of patients seen and managed in this way rated their experiences as good or excellent.[18] Several studies, based on both modelling and prospectively collected data, also suggest that approaches facilitating outpatient management (such as indwelling pleural catheters) can result in meaningful healthcare cost benefits despite often needing the ongoing use of consumables.[19 20]

Practitioners in the settings of primary care and acute care play a vital role in the success of ambulatory pleural management. Patients who have confirmed or suspected collections that do not cause considerable respiratory distress may avoid an emergency admission altogether if an urgent outpatient appointment with a pleural team can be arranged; in a retrospective analysis of new patients with pleural effusion seen over a four year period, 92% were able to avoid admission to hospital, usually after a diagnostic tap or large volume therapeutic pleural aspiration.[18] In those patients who are admitted, aspirating a large volume of fluid (rather than inserting a chest tube) may facilitate discharge more rapidly by relieving symptoms transiently before an urgent outpatient follow-up visit, at which initial results can be reviewed and further investigations and definitive management arranged. This method of management is now seen as best practice in some countries and is encouraged at a national level in the UK through incentivised reimbursement.[21]

How can recurrent pleural effusions be managed?

Control of breathlessness

For most patients the best approach is the removal of pleural fluid. In some, however, such as those who are particularly frail, alternative methods for controlling symptoms that avoid intervention may be more appropriate. Clinicians may choose to treat such patients as for chronic breathlessness with, for example, opiate based drugs such as oral morphine, a practice supported by meta-analysis data suggesting that this treatment can lead to substantial improvements in dyspnoea.[22] Caution should always be exercised in prescribing drugs with major side effects or with the potential for addiction or misuse, especially in those who already have a degree of respiratory compromise. The optimisation of treatments for underlying medical conditions, particularly those such as heart failure that might be driving effusions, is also important. The management of breathlessness in terminally unwell people, which will encompass many patients with recurrent pleural effusions, is discussed in detail elsewhere.[23]

Recurrent aspirations

The decision on how to manage a recurrent pleural effusion should be made on a case by case basis as all treatments are not suitable (or desirable) for all patients. The least invasive

Box 2 Light's criteria

Light's criteria[12] use pleural and serum measurements of protein and lactate dehydrogenase to determine whether an effusion is likely to be caused by an exudative process. The absolute levels in fluid of both measures would normally be raised in an exudate; however, if none of the following criteria are met the effusion is most likely a transudate:

- pleural fluid protein to serum protein ratio >0.5
- pleural fluid lactate dehydrogenase to serum lactate dehydrogenase ratio >0.6
- pleural fluid level more than two thirds of the normal upper value for serum lactate dehydrogenase as determined locally

Box 3 Pleural fluid tests (adapted from British Thoracic Society guidelines)[14]

Recommended for all sampled effusions

Biochemistry—lactate dehydrogenase and protein. To allow application of Light's criteria paired serum blood samples should also be sent

Microbiology—microscopy, culture, and sensitivities. Additional samples in blood culture bottles are also recommended where infection is strongly suspected

Cytology with differential cell count—refrigeration suggested if delays in processing are expected

Additional tests for selected cases

Pleural fluid pH in cases of suspected pleural infection—non-purulent samples only. Most ward based blood gas analysers are suitable for processing if a heparinised syringe is used, although local policy should be followed

Glucose—may be of use in diagnosis of rheumatoid effusions

Acid fast bacilli and tuberculosis culture, and adenosine deaminase (ADA)—in cases of suspected tuberculosis related pleuritis

Triglycerides and cholesterol—to diagnose chylothorax and pseudochylothorax

Amylase—may be useful in cases of effusions related to pancreatitis or oesophageal rupture

Haematocrit—a pleural fluid haematocrit >50% of the blood value is diagnostic of haemothorax

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.[24] This method may also be advocated in those with a particularly low frequency of fluid recurrence.

Pleurodesis and trapped lung

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 not "trapped." Trapped lung describes incomplete re-expansion and is distinct from pneumothorax due to visceral puncture or rupture, although radiologically they may appear similar, both being demonstrated by an absence of expected lung markings. Trapped lung may be indicated clinically by cough, pain, or a pulling sensation during pleural aspiration.

If there is evidence of adequate lung expansion following drainage, a chemical irritant is then inserted into the drained pleural cavity. It can be given either as a slurry through the drain or applied at the end of the thoracoscopy as a powder sprayed directly onto the pleural surfaces ("poudrage"). Data from a Cochrane meta-analysis suggest that sterile talc powder is the most effective pleurodesis agent,[25] and its use has now been adopted as standard in many parts of the world. Although debate remains as to the most effective method for delivery of talc, quoted success rates are usually around 80% at one month post-procedure.[24]

Indwelling pleural catheters

Indwelling pleural catheters are now being increasingly used and are likely to be encountered by medical practitioners across a wide range of specialties, including in the community. These tunnelled chest tubes are licensed for the drainage of all recurrent pleural effusions. The catheters can be inserted under local anaesthetic as a day case procedure, after which fluid is drawn off periodically (usually two or three times each 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 patients themselves, and when not being used the indwelling pleural catheter remains concealed under a compact dressing (fig 3⇓). Box 4 describes some tips for managing indwelling pleural catheters.

Although there is increasing evidence that indwelling pleural catheters can be used for recurrent effusions of varying cause,[26] they are typically inserted in patients with trapped lung or for cases of malignant pleural effusion, either following failed pleurodesis using talc or, increasingly, as primary treatment. The shift towards using them as primary treatment came as a result of the recently published TIME-2 trial, in which 106 patients with malignant pleural effusion were randomised to receive either a standard talc pleurodesis or an indwelling pleural catheter.[27] The study found 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 indwelling pleural catheters are both safe and effective for the long term control of effusions, sometimes extending to years, with low rates of pleural infection and hospital readmission once sited.[28 29] Smaller scale studies would also suggest that they may be used safely in those patients undergoing chemotherapy.[30]

What does the future hold for managing pleural effusions?

Although there has traditionally been a dearth of high quality evidence relating to pleural medicine, an increasing number of well conducted studies are ongoing. 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 proved malignant pleural effusion.[5] Treatments

Box 4 Tips for management of indwelling pleural catheters

- Monitor incision sites 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, 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
- The catheter can be attached to a normal underwater seal (using the correct adaptor) if continuous drainage is needed. Remember that catheters are not usually sutured to the skin so ensure adequate adhesive dressings are used if accessed for long periods
- Pleural infection associated with an indwelling pleural catheter can usually be managed without removal of the tube
- Indwelling pleural catheters are not a contraindication to chemotherapy

combining various strategies, such as placement of an indwelling pleural catheter at the time of thoracoscopy or talc slurry pleurodesis through an indwelling pleural catheter,[31 32] have 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 indwelling pleural catheters and pleurovesical automated pumps, both of which have been tested successfully in animal models.[33 34]

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A patient's perspective

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 the swimming pool seemed further away each length and recovering my breath became more and more difficult. My GP 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 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 [indwelling pleural catheter]. 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 reasonably normal lifestyle 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.

Ronald Huish, Bristol

A patient's perspective

I had just started my new job, and in an effort to keep healthy I decided to cycle to work. This proved to be more tiring than expected—I regularly attended the gym so expected it to be easy. On day 5 something definitely felt wrong; cycling home I had the most immense pain in my shoulder, getting worse to the point where I could no longer move or breathe. I was rushed to Southmead Hospital A&E.

An x ray showed that there was a large build-up of fluid around my right lung, and that I had pneumonia. A drain was inserted into the affected area; however, owing to loculation this did not drain all the fluid. I was presented with a few possible treatment options, including using special drugs to break down the pockets of fluid. Before this I was sent for a CT scan to see the extent of the loculation and help select a treatment. However the scan highlighted a large, unknown lump in my chest that needed investigation and which resulted in the need to operate. I was transferred to another hospital (Bristol Royal Infirmary) to undergo a five hour thoracotomy to remove both the fluid and the lump, which turned out to be a benign teratoma. I spent a total of two weeks as an inpatient between Southmead and BRI [Bristol Royal Infirmary] and was then signed off work for six weeks.

I was surprised when I got home how difficult I found normal everyday tasks; I needed to rest mid-shower as I couldn't breathe and I couldn't sleep flat on my bed. It was a massive shock that a normal, fit, 28 year old could be cycling to work one day and then struggling to walk down the road the next with no obvious symptoms or warning signs.

It took about six months for me to gradually get normality back; however, even now, a year later, I have pain when breathing deeply and yawning.

Lucy Crowther, Bristol

How were patients included in the creation of this article?

The structure and content of the article was discussed with individual patients during preparation of the manuscript. In addition, these patients kindly agreed to contribute short descriptions of their experiences relating to their pleural disease and treatment.

Tips for non-specialists

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

Ongoing and potential areas for future 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 six 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 malignant pleural effusion are managed. The IPC-Plus trial is a UK multicentre randomised controlled study comparing the use of indwelling pleural catheters alone with such catheters in combination with talc slurry, with completion expected in the next 12 months (ISRCTN73255764)
- The role of indwelling pleural catheters 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 indwelling pleural catheter (ISRCTN66354436)

Figures

Questions for future research

- What is the best way to identify trapped lung early?
- Are there any intrapleural agents that might be used to directly treat malignant effusions?
- Are there any bedside or simple laboratory tests that might help to identify patients with malignant pleural effusions more effectively?

Additional educational resources

Resources for healthcare professionals

British Thoracic Society Pleural Disease Guideline 2010—a comprehensive overview of the current evidence behind many aspects of pleural disease, including investigation of undiagnosed effusions, pleural infection, and interventional techniques. Likely to be of greatest interest to general clinicians

Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. *J Gen Intern Med* 2011;26:70-6—useful review of 19 studies with good figures relating to potential complications; likely to be of interest to all clinicians who are involved in the management of indwelling pleural catheters

Resources for patients

British Lung Foundation. Mesothelioma information (www.blf.org.uk/Page/Mesothelioma)—a general overview of mesothelioma for patients and their carers, with links to resources for support

MacMillan Cancer Support. Pleural effusion information (www.macmillan.org.uk/information-and-support/coping/side-effects-and-symptoms/other-side-effects/pleural-effusion.html)—a clear and accessible summary of some of the methods used to diagnose and manage pleural effusions

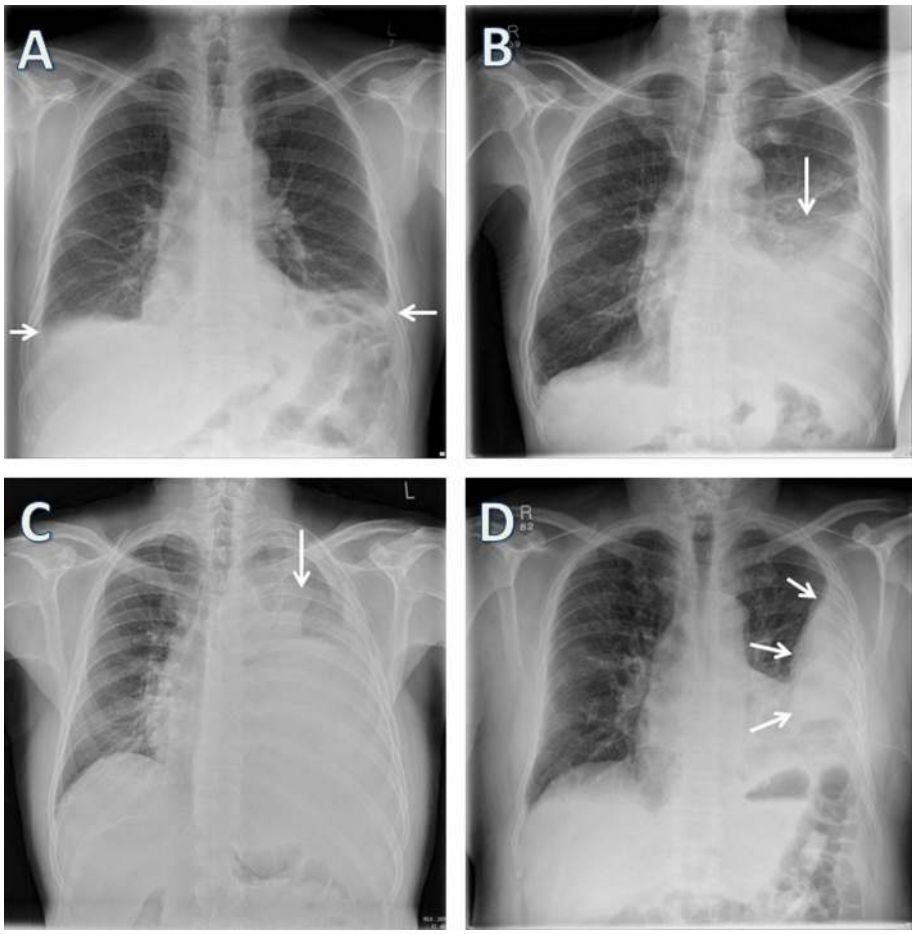

Fig 1 Varying appearances of pleural effusion. (A) Small bilateral effusions, (B) moderate left sided effusion, (C) large left sided effusion, and (D) left sided loculated pleural effusion with intercostal drain in situ

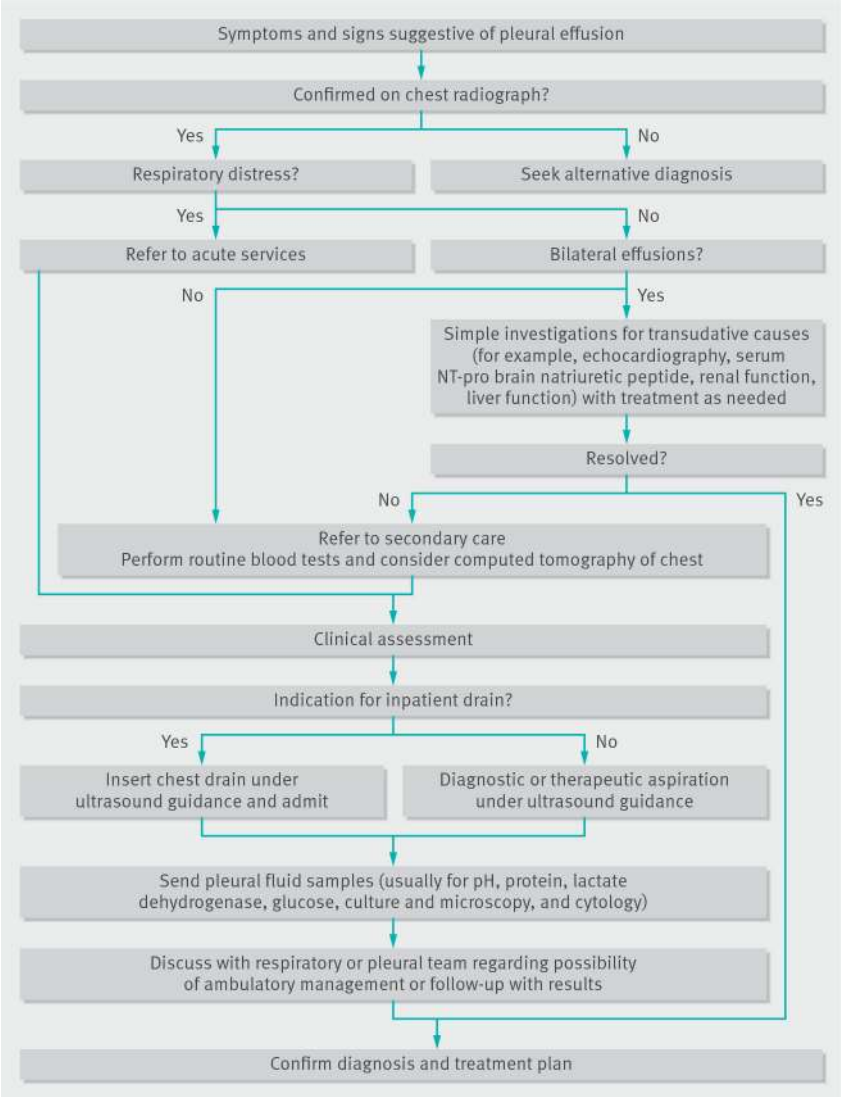

Fig 2 Suggested algorithm for early investigation of suspected pleural effusion

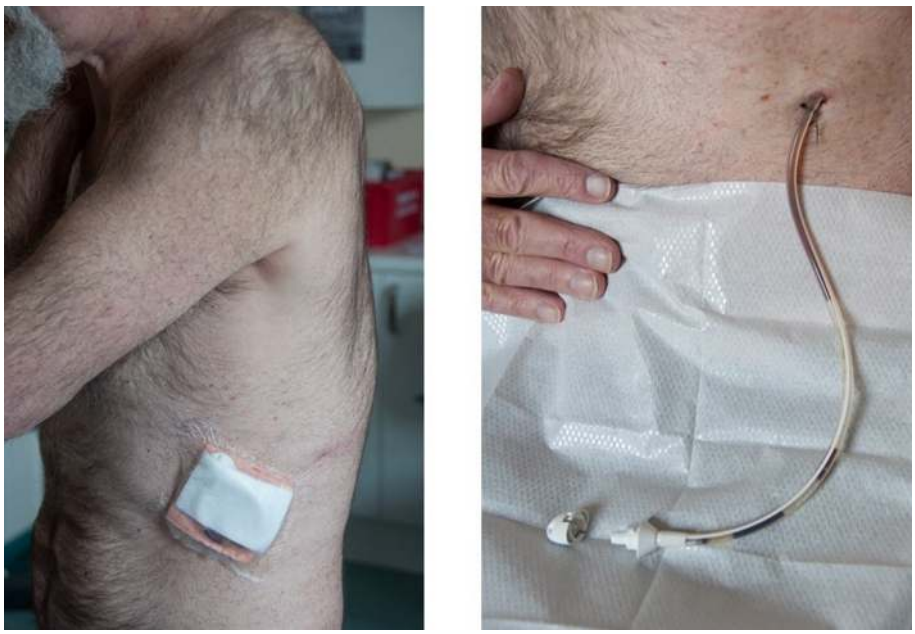

Fig 3 Indwelling pleural catheter, dressed (left) and undressed (right) before drainage