A practical approach to diagnosing pleural effusion in southern Africa

The presence of pleural effusion invariably indicates disease.

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Excessive fluid accumulating within the pleural space is a common medical affliction and invariably indicates disease.[1,2] Under physiological conditions fluid enters and exits the pleural space at the same rate.[3] The rate of production is determined by Starling's forces, i.e. hydrostatic pressure, osmotic pressure and membrane permeability, whereas the exit rate is determined by clearance through lymphatic drainage.[3] Alterations in any of these forces can lead to the formation of a pleural effusion. While the physiological amount of pleural fluid present has various positive effects on respiratory function, e.g. assisting in creating a negative intrathoracic pressure and reducing friction between pleural membranes, excessive fluid can significantly impair normal respiratory function. Once the volume of fluid in the pleural space reaches 200 - 250 ml, it is detectable on a standard PA chest radiograph (CXR). The presence of a pleural effusion can be clinically detected only after the fluid volume reaches 300 - 350 ml,[4] but in the event of small volumes the sensitivity and specificity in its detection rates remain low.[5] Because the differential diagnosis for intrapleural fluid accumulation encompasses a wide spectrum of conditions, a systematic approach to these effusions is particularly important in their investigation.

Table 1. Causes of a transudate

Frequent	• Congestive cardiac failure • Hypoalbuminaemia • Peritoneal dialysis • Liver failure
Infrequent	• Hypothyroidism • Nephrotic syndrome • Pulmonary embolism • Urinothorax • Pericardial constriction • Mitral valve stenosis

Aetiology

The causes of pleural effusions can be classified as either a transudate (Table 1) or an exudate (Table 2).[1,6] The most common causes of a transudate are congestive cardiac failure (CCF) and hepatic cirrhosis,[6] while the most common exudative effusions are caused by *Mycobacterium tuberculosis* (MTB) infection, malignancy or bacterial pneumonia.[2,6] In the case of a bilateral effusion the spectrum of differential diagnoses is narrower than that of a unilateral effusion. Bilateral effusions are commonly caused by CCF, hypoalbuminaemic states, renal failure and, rarely, malignancies, rheumatic arthritis or pulmonary embolisms. Differentiating the cause of a pleural effusion is greatly aided by careful history taking and physical examination, assisted by various targeted special investigations.[1]

Clinical presentation

Patients often present with a cough, dyspnoea and a pleuritic type of chest pain when suffering from a pleural effusion.[7] A history of cardiac, liver or renal failure may suggest a transudate, whereas a history of a recent diagnosis of a malignancy would suggest a malignant effusion. Similarly, a preceding history of deep vein thrombosis suggests an effusion related to a pulmonary embolism and constitutional symptoms of MTB, or a household contact with cavitating MTB infection could point to a tuberculous effusion. Additionally, history taking should explore recent surgery or trauma and a complete occupational history including exposure to asbestos and a review of medications used (Table 3).[1] Physical findings could also aid in the diagnostic work-up – identifying the presence of ascites may suggest MTB infection, cirrhosis or malignancies, e.g. ovarian carcinomas. The clinician usually progresses from considering the possibility of a pleural effusion on examination to confirming its presence by requesting either a CXR or performing an ultrasound examination.

Table 2. Causes of an exudate

Frequent	• Tuberculosis • Malignancy • Parapneumonic effusions
Infrequent	• Rheumatoid and other autoimmune disorders • Post-myocardial infarct syndrome • Post-coronary artery bypass • Asbestos-related effusion • Pancreatitis • Drugs (Table 3)

Radiology

Chest radiograph

The plain PA CXR, although not specific, has various features suggesting the presence of a pleural effusion. Depending on the size of the effusion, these features can vary from blunting of the costophrenic angle (Fig. 1) to loss of the diaphragmatic silhouette and, ultimately, to a complete white-out of a hemi-thorax (Fig. 2).[1] Other features that may be present are the displacement of the trachea to the contralateral side of the effusion (Fig. 2), features suggestive of a subpulmonic effusion (lateral peaking of an apparently raised hemidiaphragm) (Fig. 1) or the hazy appearance of the lung, often referred to as the 'veiled' lung.[1] The CXR can also be helpful

Table 3. Drugs associated with pleural effusions

Rare	• Amiodarone • Phenytoin • Methotrexate
Very rare	• Carbamazepine • Cyclophosphamide • Penicillamine

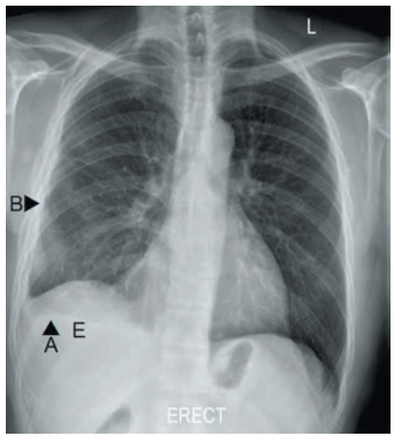

Fig. 1. A chest radiograph showing a subpulmonic effusion (E), with lateral peaking (A) of the apparent hemidiaphragm, with associated features including a steep lateral and gradual medial slope of this apparent diaphragm. Additionally, there is loss of the costophrenic angle and the effusion is visible on the lateral aspect (B).

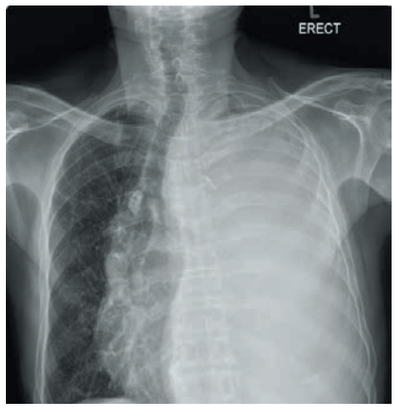

Fig. 2. A chest radiograph showing a massive left-sided effusion with midline shift to the right.

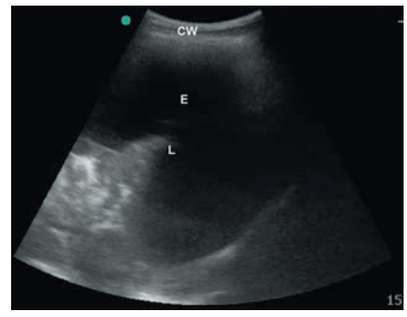

Fig. 3. This transthoracic ultrasound image clearly shows a hypo-echoic area representing a pleural effusion (E) between the chest wall (CW) and atelectatic lung (L).

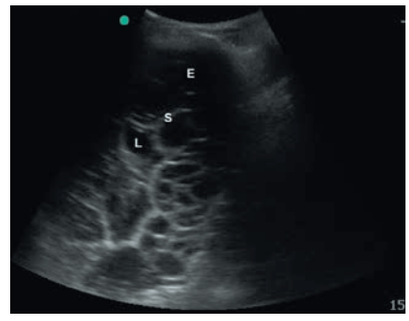

Fig. 4. A transthoracic ultrasound scan yielding evidence of a pleural effusion (E) with septations (S) and loculations (L).

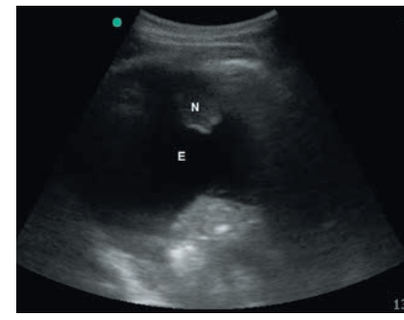

Fig. 5. A transthoracic ultrasound scan of patient with an effusion (E), where a malignant pleural nodule (N) is visible on the parietal pleura.

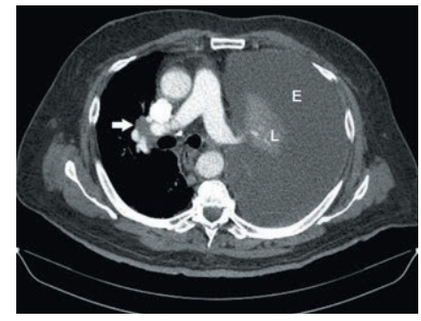

Fig. 6. A computed tomography scan showing right hilar lymph adenopathy (arrow) and a left-sided pleural effusion (E) with a collapsed lung (L).

in determining the cause of the effusion.[2] Where an effusion and a mass lesion or hilar adenopathy are present on the CXR, a malignant effusion should be included in the differential diagnosis. However, the CXR often fails in determining the presence of locutions or septations within the effusion or in the detection of pleural thickening and fibrosis. This is where either a decubitus CXR or an ultrasound examination can aid in the evaluation.[1]

Transthoracic ultrasound

Ultrasound examination is very sensitive in detecting effusions and accurate in determining the size and other features of the effusion.[8,9] It has the advantage of the instrumentation being portable and the technique safe to perform.[8] The effusion is identified as an anechoic area between the visceral and parietal pleura (Fig. 3).[10] Exudates can also display a homogeneous echogenic pattern.[1] Depending on the size of the effusion, the operator can also identify the collapsed lung in the effusion or the presence of septations (Fig. 4), loculations and pleural thickening.[10] Ultrasonic features can also suggest the aetiology of a lesion, e.g. a malignancy (Fig. 5). This technique has a superior sensitivity to computed tomography (CT) in determining subtle features of an effusion, such as pleural thickening.[8]

Computed tomography of the chest

A chest CT scan is not indicated in the initial work-up of all patients who present with a pleural effusion.[8] The CT scan allows imaging of the underlying lung parenchyma and the mediastinum, thereby assisting in determining the aetiology (Fig. 6).[6] A further indication would be a difficult-to-drain effusion; here CT scanning is helpful in determining the size and location of the effusion. A CT scan, using a contrast medium, should therefore be requested in selected cases after the initial diagnostic work-up has indicated a need for further imaging.

Thoracentesis

Indication and evaluation

Thoracentesis and fluid analysis is a low-risk, cost-effective procedure that can rapidly narrow down the differential diagnosis.[3] Therefore, it should be performed in all cases of an effusion of >10 mm on CXR or ultrasound.[6,8] An exception is a pleural effusion associated with clinical features of cardiac failure where the effusion decreases in size and fully resolves after initiation of diuretic therapy.[1,6] The initial thoracocentesis is often done for diagnostic purposes, except when the patient complains of shortness of breath at rest, where it could also be done for therapeutic benefit.

Once aspirated, fluid should be sent to the laboratory (Table 4) for cytology, cell counts, microbiology and biochemical analysis.

Macroscopic appearance

After performing a thoracocentesis the odour and macroscopic appearance should be noted. A foul-smelling odour suggestive of an anaerobic infection can guide antibiotic choice.[1] The macroscopic evaluation of the aspirated fluid frequently further contributes to narrowing down the differential diagnosis. The appearance of the aspirate is divided between that of blood stained, frank blood, serous, purulent and chylous.[1,3] Although not specific, these features may suggest an underlying cause (Table 5).

In the case of a bilateral effusion the spectrum of differential diagnoses is narrower than that of a unilateral effusion.

Routine chemistry

Laboratory tests must include pH measurement, fluid protein concentration, lactate dehydrogenase (LDH), albumin and adenosine deaminase (ADA) levels.[3,6] Concurrently, the serum protein and LDH levels should be determined for comparison with pleural fluid values.[1,3,6] This chemical analysis helps to determine whether the fluid is an exudate or a transudate by applying the modified Light's criteria (Table 6). A pleural effusion with a protein level >30 g/l together with a fluid protein ratio >0.5 is indicative of an exudate.[3] Using only protein levels to differentiate between a transudate and an exudate will erroneously result in the classification of 15% of transudates and 10% of exudates.[1] Light's criteria should therefore always be used to differentiate between transudates and exudates, especially when the fluid protein level is 25 - 35 g/l.[6] This will correctly identify all exudates, but it could classify up to 20% of transudates as exudates.[3] This error in classification can be corrected for by determining the protein gradient of the fluid to either serum protein or albumin levels. If the difference between protein levels of the effusate and serum is >31 g/l or the difference in albumin is >12 g/l, those exudates should be considered transudates.[3] These gradients should however not be used on their own to determine the classification, as this will lead to errors in up to 30% of cases.[6] The LDH level, in addition to its use as part of the Light's criteria, can also indicate the presence of empyema if it is >1 000 U/l. As part of the Light's criteria, an LDH of >2/3 of the upper limit of the laboratory normal or a fluid to serum LDH ratio of >0.6 indicates an exudate.[1]

pH

A pleural fluid pH measurement should be performed on all non-purulent effusions.[1] Where a pH value of <7.2 is found this may be indicative of a complicated parapneumonic effusion or empyema and should prompt the insertion of an intercostal chest drain to clear the fluid and obtain source control.[11,12] Other less frequent causes of a low pH include rheumatic arthritis, malignancies, oesophageal rupture and sample contamination with lignocaine. In addition to the elevated LDH and low pH values, parapneumonic effusions are neutrophil predominant.

Adenosine deaminase

Fluid ADA level is of particular use where TB is highly endemic. ADA levels >40 IU/l,[9] in conjunction with a lymphocytic predominance, is highly sensitive but may have sub-optimal specificity (70 - 90% depending on the study referred to and the cut-off point used) for TB pleural effusions.[8,9] Other causes

Table 4. Analysis of pleural fluid aspirates should include the following:

Basic	• Stains for AFB, TB culture • Bacterial MCS • Cytology • Differential cell count • ADA • LDH • Protein
Additional	• Albumin • Glucose • IFN-γ • Fungal culture • Lipid analysis • Haematocrit • Amylase • Tumour markers • Complement C4 level

AFB = acid-fast bacilli; MCS = microscopy, culture and sensitivity; ADA= adenosine deaminase; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; IFN = interferon.

Table 5. Macroscopic appearance of pleural effusions

Straw colour	• Tuberculosis • Transudates • Simple parapneumonic effusion • Benign asbestos-related effusion
Chylous	• Neoplasms • Trauma • Tuberculosis • Sarcoidosis • Amyloidosis • Neoplasm
Bloody	• Trauma • Pulmonary embolism • Post-cardiac injury
Purulent	• Tuberculosis • Empyema

Table 6. Modified Light's criteria

Pleural fluid is an exudate if one or more of the following criteria are met:

Pleural fluid
- Serum protein ratio >0.5
- Serum LDH ratio >0.6
- LDH >2/3 upper limit of normal serum LDH
- Protein >30 g/l

If only one of the above criteria is met, then calculate the fluid to serum albumin gradient
- If the albumin gradient >12 g/l, consider a transudate

LDH = lactate dehydrogenase.

Table 7. Aetiologies associated with differential cell counts

Neutrophilic	• Parapneumonitis
	• Pancreatitis
	• Pulmonary embolus
	• Malignancy (rare)
	• Acute tuberculosis
Lymphocytic	• Tuberculosis
	• Lymphomas
	• Other malignancies
	• Rheumatoid arthritis
Eosinophilic	• Drug reactions
	• Parasitic infection
	• Tuberculosis (rare)
	• Pneumothorax

of an elevated ADA include malignancies, empyema and rheumatoid arthritis (RA).[8,9] HIV infection can, however, cause false low ADA levels despite co-infection with TB.[3] In selected cases, direct measurement of unstimulated interferon-gamma (IFN-γ) levels in pleural fluid can confirm MTB infection with a sensitivity and specificity of >90%.[13,14] Unfortunately this test, despite being very sensitive, is costly and should be reserved for highly selected cases only. The IFN-γ-release assay (IGRA), which measures T cell release of IFN-γ following stimulation by antigens unique to MTB, has been proven to be ineffective and inconsistent when performed on pleural fluid.[15,16]

Additional biochemical analysis

Additional biochemical tests that are useful include pleural fluid glucose levels, cholesterol or lipid levels and amylase measurements. Pleural exudates with a glucose level <3.3 mmol/l are probably due to an empyema, RA, lupus, TB, malignancy or rarely oesophageal rupture.[3,6] With RA effusions, the glucose level is often 1.6 mmol/l.[3] An amylase measurement in pleural fluid higher than that of serum[2] suggests pancreatitis, pancreatic pseudocyst or a ruptured viscus as the cause of the exudate.[1] An elevated amylase level can also be caused by approximately 10% of malignancies. Lipid analysis of the pleural fluid can discriminate a pseudochylothorax from a true chylothorax.[2] The latter will typically have a high triglyceride level (>1.24 mmol/l) and can be excluded if the triglyceride level is low (<0.56 mmol/l).[1] A pseudochylothorax is characterised by an elevated cholesterol level (>5.18 mmol/l) in the absence of chylomicrons in the fluid.[1] A chylous effusion is usually related to malignancies, or surgically or otherwise traumatised thoracic duct or its tributaries, but it can also be caused by TB or sarcoidosis.[1]

Differential cell count

Causes of a neutrophil-predominant effusion include acute MTB infection (up to 20% of cases in some series), pulmonary embolism and benign asbestos-related effusions.[17] A pleural fluid predominated by lymphocytes occurs in various disorders including TB, lymphomas or other malignancies, RA and chylothorax.[3] Eosinophilic predominance, defined as the presence of ≥10% eosinophils, carries little diagnostic significance as >30% of these effusions remain undiagnosed, but at times these effusions are caused by air or blood in the pleural space,[3,6] drug reactions, TB and parasitic infections (Table 7).[1]

Microbiology

Microbiological evaluation of the pleural fluid should include Ziehl-Neelsen and Gram staining and liquid cultures for MTB and other bacteria.[1] Recently, the GeneXpert® test for use on pleural fluid has become available. This polymerase chain reaction (PCR)-based test is accurate, with a high sensitivity and specificity for detecting active MTB in sputum. It has the additional benefit of testing for rifampicin resistance and serves as a surrogate for determining multidrug resistance in the setting of MTB infection. However, it should not be used for the routine diagnosis of TB pleural effusion as its sensitivity is low (~25% in over 100 suspected cases of TB pleural effusion according to unpublished data by R Meldau *et al.*). An additional antigen assay for detecting *Streptococcus* pneumonia in pleural fluid is commercially available,[18] but it is not recommended for routine use because of its limited therapeutic benefit and cost.

Cytology

Cytological evaluation is particularly important if a malignancy is expected. The sensitivity of cytology on a single sample is around 60%[3] and yield increases if both cell blocks and smears are used.[6] Sensitivity is, however, dependent to some extent on the type of malignancy involved. Mesotheliomas, for instance, are only reliably detected in about 10% of cases compared with the adenocarcinoma detection rate of up to 70%.[6]

Pleural biopsy

Blind biopsy of the pleura adds little to cytological investigation in terms of diagnosing pleural malignancies. Ultrasound-guided biopsies, however, may be utilised in patients with suspected malignancies where the cytology remains negative or in cases with suspected pleural TB.[8]

Ultrasound-guided pleural biopsy

These biopsies, performed using an Abrams needle, are of greatest value in diagnosing granulomatous disorders and malignancies, including mesotheliomas. Whenever a pleural biopsy is done, tissue should be sent for TB culture smear and acid-fast bacilli (AFB) tests. Further tests should include histology, electron microscopy and bacterial cultures. When these investigations are collectively performed, biopsy has a diagnostic yield of up to 90%.[8,10] Biopsy specimens should be taken at the area of maximal pleural thickening or nodularity as identified by ultrasound.[8,10] In the event that no nodularity or thickening can be identified, a biopsy can be taken at the safest point, as determined by deepest fluid collection on ultrasound, when suspecting TB.[8] If a malignancy is suspected, the biopsy

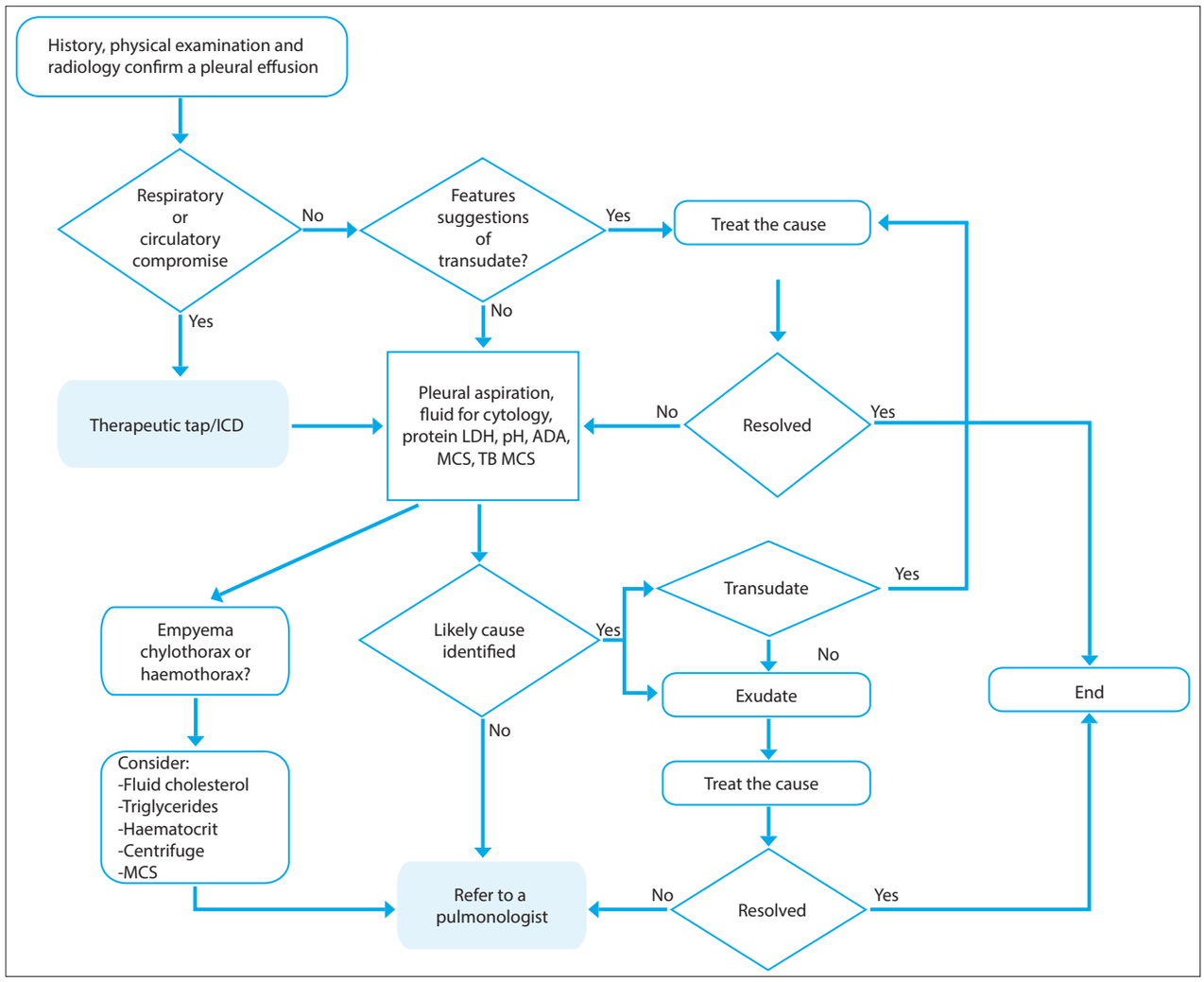

Fig. 7. An initial diagnostic approach to a pleural effusion (adapted from Maskell and Butland[1]) (MCS = microscopy, culture and sensitivity; LDH = lactate dehydrogenase; ADA = adenosine deaminase; ICD = implantable cardioverter defibrillator).

should be taken as low or near to the diaphragm as safely possible, because malignant cells accumulate at the bases. When taking a biopsy from a suspected mesothelioma, the site should be marked as there is a risk of cellular seeding through the biopsy tract. To prevent this, radiation to the site will be required within one month of the biopsy.[1] Other complications of an Abrams needle biopsy include pain, vasovagal reactions, haematomas and haemothorax.[8]

Thoracoscopy

If the cause of a pleural exudate remains unclear despite repeated thoracentesis with appropriate evaluation followed by an ultrasound-guided core needle/Abrams needle biopsy as described above, the next step would be to offer the patient a medical or surgical thoracoscopy.[8] Both these procedures, the prior performed by a pulmonologist and the latter by a thoracic surgeon, have a diagnostic yield for MTB reaching 100% and >90% for cancer, respectively.[8]

Persistent undiagnosed effusions

Despite repeated cytology, pleural biopsies and thoracoscopy, the cause of persistent undiagnosed effusions remains unknown in a small percentage of cases.[1] In this setting it is recommended that one reconsiders treatable causes such as TB, fungal infections and pulmonary embolism.[1] If these have been excluded, a watch and wait approach could be followed while offering symptomatic treatment as needed. Many of these undiagnosed pleural effusions will eventually be attributable to malignancies.[1]

A practical approach in the southern African context

Once a patient presents to the primary healthcare practitioner with a history and physical examination suggestive of a pleural effusion, a confirmatory CXR should be done. Significant shortness of breath or mediastinal displacement should prompt therapeutic drainage. In most cases, however, these features are not present, and a calculated stepwise approach to diagnosing the problem should be followed (Fig. 7). A diagnostic thoracocentesis (ideally under ultrasound guidance) should be undertaken to determine the fluid LDH, protein, and ADA levels. Furthermore, cell counts, microscopy, culture and sensitivity (MCS) tests should be performed. It has also been suggested that serum LDH and protein levels must be done for comparison. Glucose level determinations in pleural fluid can also be beneficial in some cases. The modified Light's criteria should be used to classify the fluid as either an exudate or a transudate.

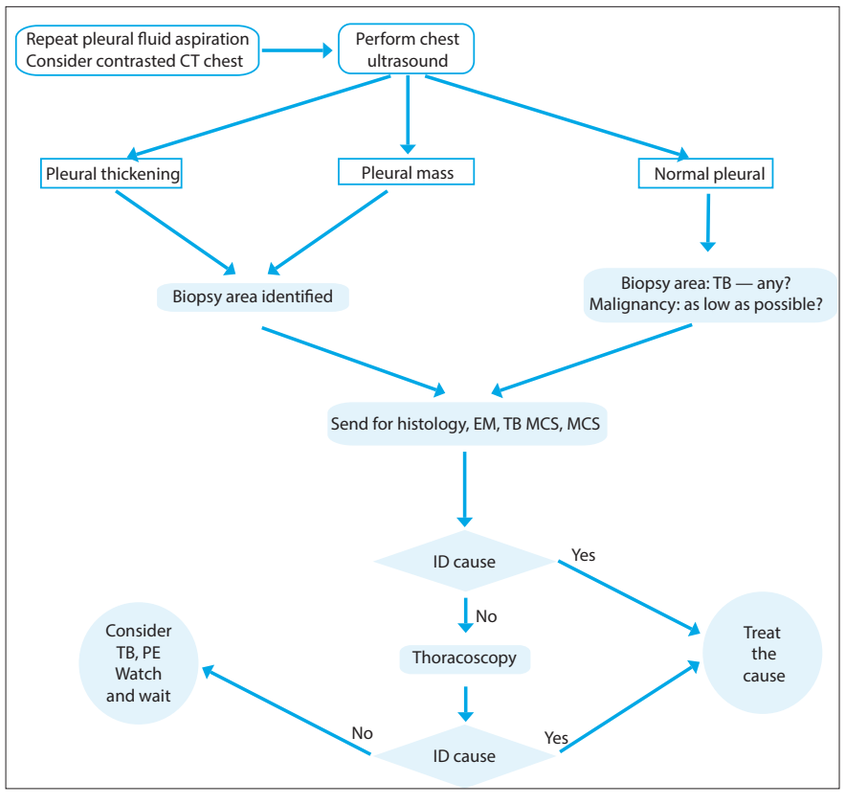

Fig. 8. A suggested diagnostic approach to an undiagnosed pleaural effusion (CT = computed tomography; PE = pleural effusion; EM = electron microscopy; MCS = microscopy, culture and sensitivity).

With a transudate, it is reasonable to treat the most likely cause and review the resolution of the effusion. Most exudates in southern Africa are secondary to pneumonia, TB and pleural malignancies. Pleural TB, for example, classically presents with a straw-coloured, lymphocyte-predominant exudate with an ADA >40 IU/l. It may be reasonable to treat and review the patient (even in the absence of microbiological confirmation), but the drawback of this approach is the potentially unnecessary drug toxicity and failure to treat appropriately in the case of drug-resistant TB. The latter is a serious consideration, given that 8 - 10% of TB cases will be drug resistant. Purulent effusions with a low pH should be drained using an intercostal drain or thoracic surgery, and appropriate antibiotic treatment started. Cases of suspected malignant effusions warrant specialist referral. Patients with undiagnosed, chylous or haemorrhagic effusions should also be referred for further evaluation, and should undergo additional investigations, which may include a repeat thoracocentesis, ultrasound-guided pleural biopsy or thoracoscopy (Fig. 8).

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Summary

- Excessive fluid accumulating within the pleural space is a common medical problem and invariably indicates disease.
- A structured approach with thoracocentesis as the first step is indicated in almost all cases.
- An effusion should be classified as either an exudate or a transudate using the modified Light's criteria.
- Transudates may be followed up conservatively (awaiting resolution), but exudates need further evaluation of the pleural fluid and possible sampling of pleural tissue.