REVIEW

Pleural effusion

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Pleural disease remains a commonly encountered clinical problem for both general physicians and chest specialists. This review focuses on the investigation of undiagnosed pleural effusions and the management of malignant and parapneumonic effusions. New developments in this area are also discussed at the end of the review. It aims to be evidence based together with some practical suggestions for practising clinicians.

Pleural effusions are a common medical problem and a significant source of morbidity. There is wide variation in management despite their significant prevalence, partly because of the relative lack of randomised controlled trials in this area. This review considers:

- The approach to the investigation of the undiagnosed pleural effusion.
- Malignant pleural effusions including evaluation of the different sclerosants.
- Pleural infection including the possible role of fibrinolytics or surgery.
- New developments including new pleurodesis targets and treatments, problems with pleural pH and talc particle size, new mesothelioma markers, and multicentre trials on fibrinolytics.

INVESTIGATION OF AN UNDIAGNOSED UNILATERAL PLEURAL EFFUSION

Background

Pleural effusions suggest pulmonary, pleural, or extrapulmonary disease. A systematic approach to investigation is needed because of the extensive differential diagnosis. An accurate drug history is necessary (box 1).

The pathogenesis may involve increased pleural membrane permeability or pulmonary capillary pressure or decreased negative intrapleural or oncotic pressure or obstructed lymphatic flow. Pleural effusions can be transudates (the balance of hydrostatic forces favours pleural fluid formation) or exudates (because of change of the pleural surface and/or permeability of the capillaries) (see table 1 for causes).[1 2]

Pleural analysis

Appearance

Thoracocentesis should be performed for protein, LDH, pH, Gram stain, AAFB stain, cytology, and microbiological culture using sterile vials and blood culture bottles to increase microbiological yield. The appearance and odour of the pleural fluid may be helpful diagnostically and should always be recorded in the medical notes. A pleural:serum packed cell volume >0.5 shows a haemothorax with <1% being not significant.[3]

Exudate compared with transudates

Classically, exudates having a protein level >30 g/l and transudates <30 g/l. Light's criteria will enable differentiation more accurately when the pleural protein is unhelpful (box 2).[4] Occasionally, Light's criteria will label an effusion in a patient with left ventricular failure taking diuretics an exudate in which case clinical judgement is required.

Differential cell counts

Differential cell counting adds little diagnostic information. Pleural lymphocytosis is common in malignant and tuberculous effusions but can also be attributable to rheumatoid disease, lymphoma, sarcoidosis, and chylothorax.[5] Eosinophilic pleural effusions are often benign but can be attributable to underlying malignancy in up to 10% of cases and therefore still needs to be investigated fully.[4] Benign causes include parapneumonic effusion, benign asbestos pleural effusion, Churg Strauss, pulmonary infarction, parasitic disease, and drugs. Coronary artery bypass grafting (CABG) can often cause left sided, haemorrhagic, eosinophilic pleural effusions in the early stages followed by small lymphocyte predominant effusions in the later stages.[6]

pH

Normal pleural pH is slightly alkalotic (about 7.6) because of bicarbonate accumulation. A pleural fluid pH<7.2 with a normal blood pH suggests the same diagnoses as a low pleural glucose especially pleural infection (see later).[7] Oesophageal rupture, collagen vascular diseases, and malignancy are other causes.[8] A pH<7.3 can be associated with poorer outcome in malignancy.[8]

Cytology

Malignant effusions can be diagnosed by one pleural fluid cytology specimen in 60% of cases for carcinomatous effusions but only 30% for mesothelioma.[9–11] This yield is increased only slightly if second or third cytology specimens are sent.[12] The cytological yield is higher for adenocarcinoma and when smears and blocks are used.[13] Immunohistochemical epithelial and glandular markers can help confirm epithelial malignancy and differentiate mesothelioma from adenocarcinoma.[14]

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Box 1 Drugs most commonly implicated in pleural effusions

- Amiodarone
- Nitrofurantoin
- Phenytoin
- Methotrexate
- Penicillamine
- Cyclophosphamide

Imaging

About 200 ml of pleural fluid is detectable on PA chest radiography whereas only 50 ml of fluid is detectable on a lateral film.[15] Lateral decubitus films can differentiate pleural thickening and fluid. In the supine position (for example, ventilated patient) free pleural fluid layers out posteriorly as a hazy opacity of one hemithorax with preserved vascular shadows on chest radiography.[16]

Ultrasound is more accurate for estimating pleural fluid volume and aids thoracocentesis.[17] Ultrasound is also useful in showing septations and echogenicity (correlating with an exudate) and differentiates between pleural fluid and thickening.[18] It is portable and position flexible.

With computed tomography, malignant disease is more probable in the presence of Leung's criteria: nodular, mediastinal and circumferential pleural thickening, and parietal pleural thickening >1 cm (see fig 1).[19] Computed tomograms should be contrast enhanced and performed before drainage for better vision of the pleura.[20] This will also allow a subsequent biopsy of the pleura to be performed safely. Occasionally, if there are several litres of fluid in the chest cavity, it might be reasonable to drain off some of the fluid before the scan, to permit better visualisation of the underlying lung.

Histological examination

Percutaneous pleural biopsies

Percutaneous pleural biopsies should be performed on patients with undiagnosed pleural exudates with non-diagnostic cytology and a clinical suspicion of tuberculosis (TB) or malignancy. All biopsy (and aspiration) sites should be marked with Indian ink, as tumour seeding occurs in about 40% of the patients with mesothelioma without local radiotherapy to biopsy sites.[21]

Pleural biopsy

Blind pleural biopsy (via Abrams' needle) increases the diagnostic yield over cytology alone by only 7%–27% for malignancy.[11 22] At least four samples from one site only are needed for optimal yield.[23] 10% formaldehyde should be used for histology and sterile saline for TB culture. An extensive review shows a yield of 57% for malignancy.[24] Complications include site pain (1%–15%), pneumothorax (3%–15%, rarely needing drainage), vasovagal reaction (1%–5%), haemothorax (<2%), site haematoma (<1%), and transient fever (<1%).[24]

However, a recent randomised trial has confirmed the superiority of image guided cutting needle biopsy of focal abnormal areas on contrast enhanced computed tomography over blind biopsy.[25] Pleural malignancy often occurs near the midline and diaphragm, which are inadvisable for closed biopsy but amenable to image guided biopsy.[25 26] Recent studies have confirmed the high sensitivity (86%–93%) and specificity (100%) of this approach for mesothelioma.[26]

In the authors' opinion, blind pleural biopsy no longer has a place in the investigation of malignant pleural disease (although it may be a reasonable investigation in suspected TB pleuritis, where it has a yield of over 75%[24]).

Box 2 Light's criteria

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

- Pleural fluid protein divided by serum protein >0.5
- Pleural fluid LDH divided by serum LDH >0.6
- Pleural fluid LDH >two thirds the upper limits of normal serum LDH

Table 1 Causes of pleural effusions

Transudates	Exudates
Frequent:	**Frequent:**
Left venticular failure	Malignancy
Liver cirrhosis	Parapneumonic effusions
Hypoalbuminaemia	
Peritoneal dialysis	**Less common:**
	Pulmonary infarction
Less common:	Rheumatoid arthritis
Hypothyroidism	Autoimmune diseases
Nephrotic syndrome	Benign asbestos effusion
Mitral stenosis	Pancreatitis
Pulmonary embolism	Post-myocardial infarction syndrome
Rare:	**Rare:**
Constrictive pericarditis	Yellow nail syndrome
Urinothorax	Drugs
Superior vena cava obstruction	Fungal infections
Ovarian hyperstimulation	

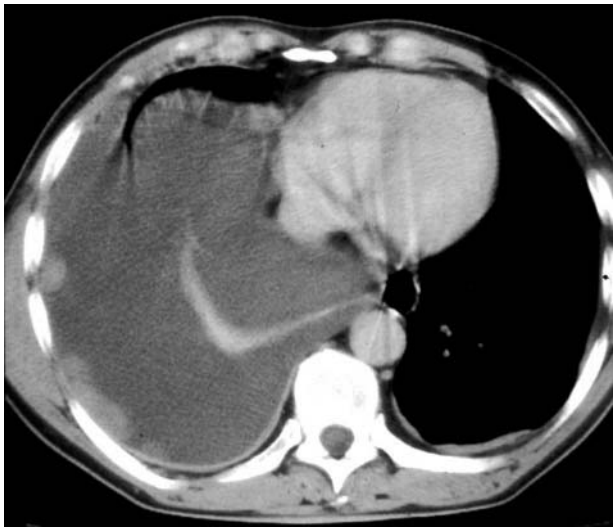

Figure 1 Computed tomography with contrast enhancement showing malignant nodular circumferential parietal pleural thickening.

Thoracoscopy

Thoracoscopy is used when less invasive techniques have not been diagnostic and the patient is fit enough. Fluid can be removed and pleurodesis performed with a high diagnostic yield (95% for malignancy).[27] A recent study has highlighted that medical thoracoscopy, even when initially set up in a new centre, gives excellent diagnostic yield (92%) with minimal complications.[28]

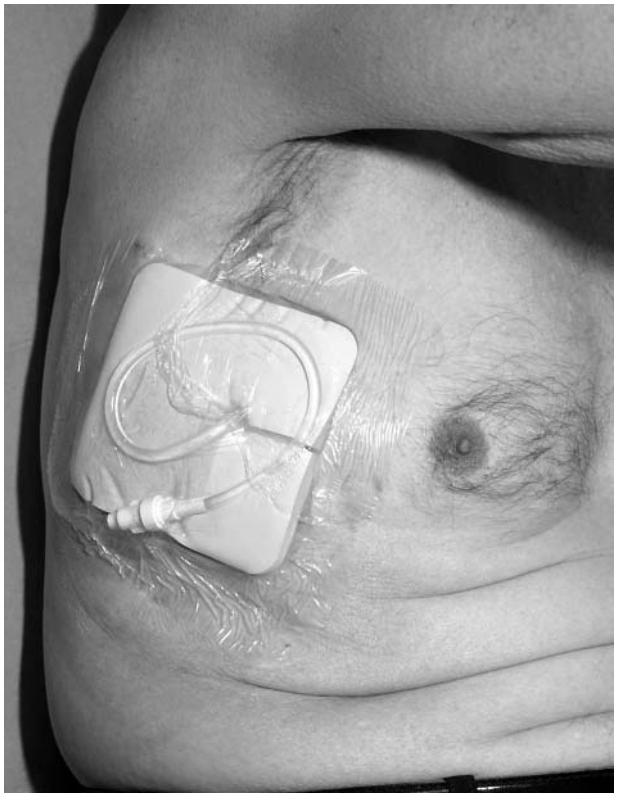

Figure 2 An indwelling (Pleurx) catheter.

Bronchoscopy
Bronchoscopy is only recommended if there is haemoptysis or signs of endobronchial obstruction. In pleural effusion without these other features, it has a very low diagnostic yield.[29]

Diagnoses not to miss and undiagnosed effusions
Tuberculous pleurisy
In TB effusions, fluid smears and culture have a low yield (10%–20% and 25%–50% respectively). Pleural biopsy histology and culture improves the diagnostic yield to about 90%.[30] Pleural fluid adenosine deaminase (ADA) may be raised but is non-specific or negative in HIV infection and only of value in high endemic areas.[31] Anti-TB treatment is reasonable to consider in the undiagnosed recurrent effusion with a positive tuberculin test (positive in 70% of TB effusions) with a lymphocytic exudates.[5]

Pulmonary embolism
Small pleural effusions are present in up to 40% of cases of pulmonary embolism, often haemorrhagic exudates.[5] A pleural RCC $>10^5/mm^3$ suggests pulmonary infarction, trauma, or malignancy.[3] The effusions have no specific characteristics and the diagnosis must be pursued on clinical grounds with a high index of suspicion and reconsidered in the context of the undiagnosed effusion as it is treatable.[5 32]

Undiagnosed effusion
In 15% of cases, the diagnosis will still be unclear despite repeated cytology and pleural biopsy.[22] As well as TB pleuritis and pulmonary embolism, fungal infection should be reconsidered as they are treatable.[32] However, underlying malignancy is often responsible and thoracoscopy may be needed if the patent is fit enough.

Less common diagnoses
Chylothorax and pseudochylothorax
True chylous effusions result from disruption of the thoracic duct or its tributaries. Malignancy (particularly lymphoma) or trauma are the commonest causes.[32] Chylothorax (triglycerides usually >1.24 mmol/l with chylomicrons) must be distinguished from pseudochylothorax (cholesterol >5.18 mmol/l), cholesterol crystals but no chylomicrons) often because of chronic rheumatoid pleurisy.[33]

Rheumatoid arthritis
Rheumatoid effusions occur 5% more often in men and are unlikely with a pleural glucose >1.6 mmol/l.[34] Pleural fluid C4 complement levels <0.04 g/l may be suggestive but rheumatoid factor mirrors serum levels and is non-specific.[34]

Systemic lupus erythematosus
Fifty per cent of patients with systemic lupus erythematosus have (often bilateral) pleural disease at some point. LE cells in pleural fluid are diagnostic.[35] Pleural fluid ANA is not helpful as it mirrors serum values.[34] However, pleural ANA in the absence of clinical systemic lupus erythematosus may be attributable to underlying malignancy.[36]

HIV infection
Pleural effusion occurs in up to 25% of HIV inpatients and is usually attributable to parapneumonic effusion, TB, Kaposi's sarcoma, or less commonly lymphoma.[37] Bacterial pneumonia, the commonest cause, carries a 10% inhospital mortality.[38]

Benign asbestos pleural effusion
Benign asbestos pleural effusions occur within 20 years after exposure.[39] Typically, there is a small, asymptomatic, haemorrhagic effusion resolving within six months leaving residual diffuse pleural thickening.[40] Diagnosis only becomes clear after prolonged follow up.

Drug induced pleural effusion
An increasing number of drugs are associated with pleural effusion (see box 1). A useful resource is http://www.pneumotox.com.

Nitrofurantoin, dantrolene, valproate, propylthiouracil, and isotretinoin have all been specifically associated with pleural fluid eosinophilia (>10%). Only nitrofurantoin, dantrolene, and valproate have been also associated with peripheral eosinophilia.[41] Of this group, nitrofurantoin can be discriminated by its unique association with interstitial changes.

Drug induced lupus pleural effusions tend to be exudates with a pleural fluid ANA ratio ⩾1.0. There may be diagnostic LE cells.[42] Antihistone antibodies are positive with normal complement levels and negative double stranded DNA.[43]

MALIGNANT PLEURAL EFFUSION
Pathophysiology and presentation
Malignant pleural effusions imply advanced disease and shortened survival in cancer patients.[44] Lung and breast cancer account for 50%–65% of such effusions.[45]

The number of parietal lymphatics (and hence pleural fluid absorption) is maximal near the mediastinum and diaphragm.[46] Necropsy studies have confirmed the contributory role of lymphatic obstruction as well as haematogenous spread.[44] Vascular endothelial growth factor (VEGF) is a potent inducer of microvascular permeability, angiogenesis, and chemotaxis and may be involved in tumour growth and generation of malignant effusions.[47 48]

Massive pleural effusions are most commonly malignant in origin.[49] Dyspnoea is the commonest presenting symptom and may be multifactorial in origin: reduced compliance,

Table 2 Staging and biochemistry of parapneumonic effusions

Stages	Macroscopic appearance	Pleural fluid characteristics	Comments
Simple parapneumonic	Clear fluid	pH>7.2	Normally resolves with antibiotics alone.
		LDH<1000	Drain if required on symptomatic grounds
		Glucose>2.2 mmol/l	
		No organisms on culture or gram stain	
Complicated parapneumonic	Clear fluid	pH<7.2	Requires chest tube drainage
	cloudy/turbid	LDH>1000	
		Glucose<2.2 mmol/l	
		May be positive Gram stain/ culture	
Empyema	Frank pus	May be positive Gram stain/ culture	Requires chest tube drainage
			No additional biochemical tests necessary on pleural fluid

diaphragmatic involvement, mediastinal shift, and volume loss stimulating stretch receptors. There may be chest pain (because of pleural, rib, or intercostal structure involvement) or constitutional symptoms.

Thoracocentesis

Repeated aspiration may be the best option if life expectancy is very short and performance status poor especially if there have been previous failed tube drainage/pleurodesis.[50]

Pleurodesis

Pleurodesis requires an inflammatory reaction and coagulation activation with fibrin deposition.[51] Ccorticosteroids may reduce the effectiveness of pleurodesis in animal studies although evidence for NSAIDs doing the same is lacking.[52] Two studies have shown at least similar success rates with small bore (10 F–14 F) compared with large tubes (24 F–38 F) with sclerosants with less discomfort although small numbers were assessed.[53 54] Smaller bore tubes are favoured because of reduced discomfort, ease of insertion, and similar efficacy.

The commonest reason for failed pleurodesis is failed apposition of the pleural surfaces because of unexpanded lung because of trapped lung, airflow obstruction, loculations, or persistent leak. Radiological confirmation of re-expansion is a more relevant predictor of success than drainage volume.[55] Re-expansion pulmonary oedema is unlikely if <1.5 litres is removed at one time and may be related to reperfusion injury to hypoxic lung, increased capillary permeability, or interleukin 8 release.[56]

Chest pain occurs variably after instillation of the sclerosants from 7% (talc) to 40% (doxycycline).[57] A dose of 150 mg intrapleural lidocaine does not even approach toxic levels in the serum (>3 μg/ml) reaching 1.3 μg/ml in one study.[58] Higher doses up to 250 mg were also within therapeutic range.[59] Other premedication and sedation is indicated but has not been studied in pleurodesis.

Sclerosant types

Talc is the most favoured sclerosant with the highest success rate (about 90% in studies).[60] It has been used since 1935, either as a poudrage at thoracoscopy or slurry via tube with

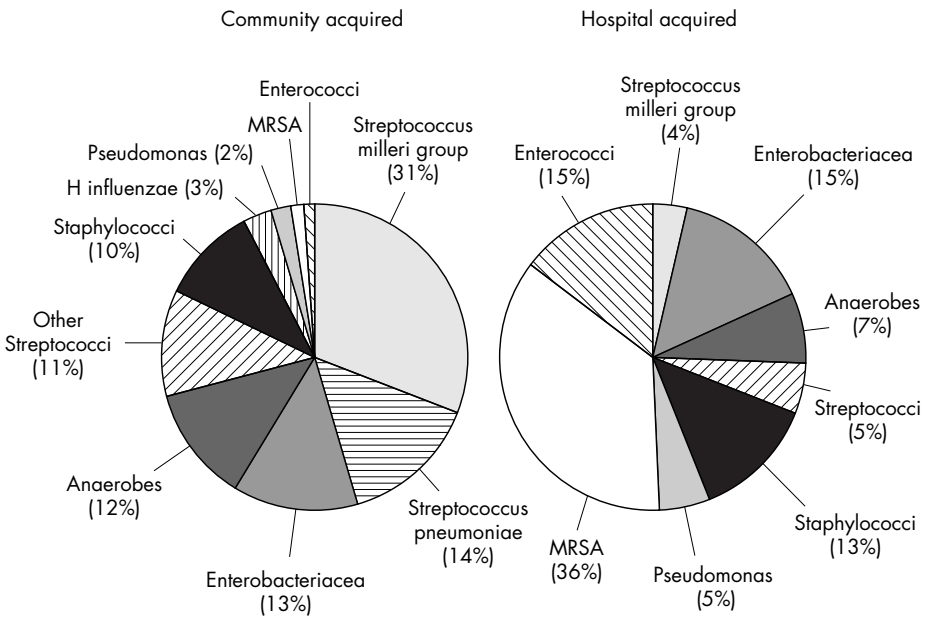

Figure 3 Causes of community acquired and hospital acquired infection.

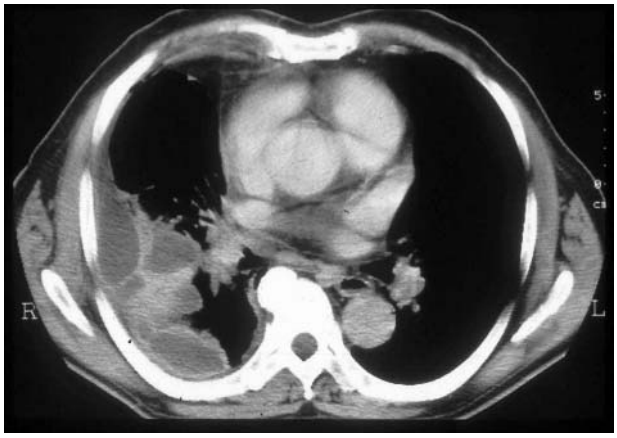

Figure 4 Contrast enhanced computed tomography showing multi-loculated empyema with ''split pleura sign'' (enhanced pleural tissue noted on both parietal and visceral surfaces).

equal efficacy.[61] One study favoured talc over bleomycin but did not reach significance.[62] Side effects include fever, chest pain, and occasional episodes of ARDS or acute pneumonitis that may be dose and particle size related (see below).[60]

A recent randomised trial of 48 patients has shown the importance of talc particle size in the incidence of complications.[63] European ''graded talc'' (Novatech, Grasse, France) contains less than 50% of particles smaller than 20 μm, whereas USA and UK ''mixed talc'' contains 50% less than 10 μm (Thornton and Ross, Huddersfield, UK). Mixed talc resulted in worsening gas exchange (A-a gradient change) and a much greater rise in fever and C reactive protein. A further randomised trial of 20 patients with ''mixed talc'' showed a greater DTPA clearance than with tetracycline consistent with less lung inflammation.[63]

Of the other agents used, tetracycline is reasonably effective (about 65% success), cheap, and safe although often now not available in the UK. Fever and pleuritic chest pain can occur with optimal doses of 1–1.5 g.[59 64–66] Bleomycin is limited by its cytotoxicity and cost (£68.75 per 60 unit dose) although its efficacy is good (about 61% success).[62]

There are no data to support patient rotation for tetracycline class agents although in the USA many still undertake this when using talc slurry. In tetracycline class studies, this did not improve distribution or success rate.[67] In practice, if good pleural apposition has been achieved and the chest radiograph confirms fluid removal then drains can be removed within 24–48 hours.

In summary, the authors recommend using calibrated talc as the sclerosant and to consider tetracycline (if available) only for failed talc pleurodeses.

Fibrinolytics (see later for detailed discussion in pleural infection)

There is a limited evidence base in the context of malignant effusion. In three non-randomised studies in multi-loculated malignant effusion, radiological improvement and improved drainage was noted with the chosen fibrinolytic (streptokinase or urokinase) in a significant proportion.[68–70] However, the studies were uncontrolled and underpowered.

A long term tunnelled indwelling pleural catheter (Pleurx, Denver Biomaterials, Golden, CO) is a safe and effective alternative to reduce dyspnoea, maintain quality of life, and reduce admission in recurrent malignant pleural disease with/without trapped lung. A retrospective review has highlighted the safety and reductions in hospital stay (seven days less) using such catheters with no differences in mortality or morbidity.[71] Only 8% developed malfunctioning catheters, with pleural infection in 5%. In practice, such catheters can reduce need for re-admission with benefits to the patient allowing them to stay at home with district nurse or outpatient management and cost savings by reduction in bed days (fig 2).

Pleurectomy is invasive (10%–13% mortality) and can be complicated by empyema, haemorrhage, and respiratory failure.[72] VATS pleurectomy negates thoracotomy and can be effective.[73] Pleuroperitoneal shunting is no longer widely used, probably because of its high rate of blockage (25%), infection, and tumour seeding.[74]

PLEURAL INFECTION

Pleural infection (first described in 500BC) was treated by open drainage until the 19th century changing to closed drainage after 1919.[75] Currently, in the UK, up to 40% of empyema patients require surgery because of failed tube drainage and 20% still die.

Pathogenesis

Parapneumonic effusions occur in up to 57% of cases although primary empyema can occur de novo without pneumonia.[76] Empyema development is a progressive process from a simple exudate (''simple parapneumonic effusion''), to a fibrinopurulent stage (''complicated parapneumonic effusion'' before frank pus or ''empyema'' develops) then finally an organising stage with scar tissue (see table 2).

In the ''simple'' stage increased capillary vascular permeability and proinflammatory cytokine production occurs.[77] The non-viscous exudate has a low white cell count and lactate dehydrogenase (LDH) level, normal pH and glucose levels, and no bacteria. Antibiotic treatment alone here may suffice.[76] Increasing fluid and bacterial invasion accelerate neutrophil migration and coagulation cascade activation leading to fibrinous loculations. Neutrophil phagocytosis and bacterial death amplify the inflammatory process with increased lactic acid production, glucose metabolism, and a rise in LDH levels, with a fall in pH, leading to a fibrinopurulent collection (pH$<$7.20, glucose $<$2.2 mmol/l and LDH $>$1000 IU/l).[77] Fibroblast proliferation leads to a pleural peel restricting lung function and re-expansion leaving a persistent pleural space with infection risk.

Microbiology

The microbiology of community acquired pleural infection is different to that of hospital acquired (see fig 3). Overall currently, aerobes (especially Gram positive) are the most abundant particularly *Streptococci milleri* and *Staphylococcus aureus*.[78] *S aureus* often occurs in traumatic, nosocomial, immunocompromised, or postoperative settings.[79] Gram negative aerobes (*Escherichia coli, Pseudomonas spp, Haemophilus influenzae*, and *Klebsiella spp*) also occur usually in mixed growths. Anaerobes are on the increase (12%–34% of positive fluid culture, 14% alone without aerobes) presenting insidiously, with less fever, greater weight loss, often after aspiration pneumonia or with poor dental hygiene.[78]

Diagnosis and staging

The presence of chest radiological infiltrates and pleural fluid may suggest pleural infection. Empyema should be suspected after failure to respond to appropriate antibiotics. Lateral chest radiograph may show pleural fluid not visible on the PA chest radiograph.[76] Ultrasound enables exact location of any fluid collection and permits thoracocentesis.[17]

Ultrasound and computed tomographic appearances do not correlate with the biochemical staging of pleural infection, but pleural thickness on contrast enhanced computed tomography can correlate with purulence.[80] Contrast enhanced computed tomography may help differentiate

empyema from a lung abscess.[81] Empyemas are usually lenticular compressing the lung parenchyma with a characteristic ''split pleura'' sign (see fig 4) caused by enhancement of both parietal and visceral pleural surfaces, and their separation. Contrastingly, lung abscesses have an indistinct boundary between lung parenchyma and collection.[82]

There are no clinical or radiological features that discriminate between the three stages of pleural infection or which predict success with antibiotic alone or need for surgery. Pleural fluid characteristics are the most helpful in guiding management. Small effusions, <10 mm thickness on decubitus chest radiography will usually resolve with antibiotics alone.[76]

Chest tube drainage

Delayed tube drainage is associated with increased admission time, morbidity, and possibly mortality.[78] Misdiagnosis, incorrect antibiotics, and suboptimal tube placement can promote progression of pleural infection.[83]

Frankly purulent or turbid/cloudy fluid on aspiration shows the need for prompt tube drainage.[76] Purulent fluid occurs more often in tube non-responsive, surgically treated and non-surviving patients.[84] A positive Gram stain shows bacterial invasion and the need for tube drainage although anaerobes are not readily cultured.[76]

A meta-analysis has confirmed pleural fluid pH (rather than LDH or glucose) as the most useful parameter predicting the need for tube drainage. A pleural pH of <7.2 was the best indicator. Earlier tube drainage may be needed in the elderly patient with comorbidity.[85] Pleural fluid for pH should be collected anaerobically with heparin (without lidocaine, which is acidic) and then measured in a blood gas analyser (unless frank pus) and not litmus paper or a pH meter.[86] Pleural pH is specific in predicting the need for tube drainage although less than 100% sensitive and does not predict need for surgery. Therefore, some patients with initial pleural pH>7.2 will fail to improve and need surgery despite tube drainage.[84] Moreover, a recent case series of seven patients with complicated parapneumonic effusion has highlighted that pleural pH varies dramatically between locules up to 10-fold differences in one case emphasising its limitations and that clinical progress remains paramount.[87]

Loculation on chest radiogarphy or ultrasound is associated with poorer outcome and may require tube drainage. Larger pleural collections (>40% hemithorax) are more likely to require surgery.[88]

Key points

- Use Light's criteria to differentiate accurately exudates from transudates.
- Check pleural pH in all non-purulent pleural effusions and drain if <7.2 and pleural infection suspected but remember isolated pH may not be fully representative if multi-loculated
- Send pleural fluid in both sterile and blood culture bottles to increase microbiological yield
- Cytology will be non-diagnostic in 40% of cases of malignant pleural effusions. In this setting, contrast enhanced computed tomography is more helpful when fluid is still present to permit better imaging of the pleura and identify the best site for biopsy
- Image guided cutting needle biopsies are superior to Abrams' needle pleural biopsy for diagnosing malignancy
- Always consider pulmonary embolism and TB in persistent unexplained effusions as treatable, although undiagnosed pleural malignancy is often the reason
- Always consider drug induced pleural disease and refer to http://www.pneumotox.com if in doubt
- Pleural lymphocytosis is common in malignancy and TB. Always consider malignancy in eosinophilic effusions
- Always mark aspiration/biopsy sites if mesothelioma is suspected with Indian ink to allow radiotherapy to prevent seeding. If necessary, radiotherapy should be performed within six weeks of the procedure
- Use ''graded'' or ''calibrated'' talc and not ''mixed'' or ''uncalibrated'' talc to reduce risks of serious side effects.

Drain size and management

Image guided small bore catheters are effective as a primary drainage procedure or as rescue treatment when larger tubes have failed with low complication rates.[89] Large bore tubes are used more for draining thick pus, but no trials have assessed this.

There is no good evidence for flushing or suction although both are regularly used.[90] Regular flushing (30 ml saline every six hours) of small tubes has been used in many studies but not for large bore tubes because of infection risks with disconnection.[89]

Tube patency can be confirmed with saline flushes. If poor drainage persists, imaging (ideally contrast computed tomography) will assess tube position or distortion and loculation. However, computed tomography cannot differentiate early and late fibrinopurulent stages and computed tomographic pleural thickness does not predict outcome from tube drainage.[84]

Antibiotics

Aerobes and anaerobes isolated from pleural infection can be penicillin resistant but β-lactams are recommended for pneumococcal and *Streptococcus milleri* infections.[91] Penicillins and cephalosporins penetrate to the pleural space well negating the need for intrapleural delivery.[92] Aminoglycosides penetrate poorly and are inactivated by acidosis.[92]

For community acquired pleural infection, a second generation cephalosporin or an aminopenicillin in combination with a β-lactamase inhibitor or metronidazole (for coexistent penicillin resistant aerobes and anaerobes) is recommended.[93] Other options include clindamycin monotherapy or combined intravenous benzyl penicillin and a quinolone. Macrolides are not usually needed as *Legionella* and *Mycoplasma pneumoniae* rarely lead to empyema.

In hospital acquired pleural infection, recommended antibiotics include antipseudomonal penicillins, carbapenems, or third generation cephalosporins.[92] Anti-staphylococcal cover (including MRSA cover) is often required.

In the authors' centre, the empirical antibiotic regimen is as follows (although local regimens obviously require close liaison with microbiologists and appreciation of differences in resistance patterns):

- Community acquired:
  - intravenous cefuroxime and metronidazole or
  - oral augmentin
- Hospital acquired:
  - intravenous vancomycin, ciprofloxacin, and metronidazole

There is no good evidence on length of antibiotic treatment although this is often continued for several weeks.[93] Efficient pleural drainage may pemit shorter antibiotic treatment.

Fibrinolytics

Intrapleural fibrinolytics were first used in 1949 with significant side effects because of impurities.[94] More recently, improved pleural drainage by several observational studies and small controlled trials including four randomised trials.[95–98] All four studies were inadequately powered to assess the main end points of mortality and surgery rates. Intrapleural fibrinolytics increase pleural fluid production so drainage cannot be properly assessed in these trials. Fever and pleural pain have been described with intrapleural delivery.[99 100] Transient disorientation, cardiac arrhythmia, and ARDS have occasionally been reported.[68]

The recently reported MRC/BTS UK controlled trial of intrapleural streptokinase for pleural infection (MIST1), assessed the efficacy of intrapleural streptokinase (250000 IU twice daily for three days) compared with placebo in complicated parapneumonic effusions. This showed no difference in the primary end point, mortality, or need for surgery at three months, between the two groups.[101] Moreover, there was no benefit in any subgroup or the secondary end points, radiographic improvement, and length of hospital stay. As a result of this study, it is the authors' practice not to prescribe intra-pleural streptokinase for any patient with pleural infection.

Recently, there has been interest in combining a fibrinolytic with a DNAse that can reduce viscosity in vitro.[102] MIST2 will assess the possible benefits of combined DNAse and alteplase in pleural infection based on the hypothesis that they can work synergistically: the DNAse reducing the effusions viscosity and the fibrinolytic breaking down the loculations.

Other issues

In persistent pleural sepsis, computed tomography of the thorax may be helpful confirming chest tube position, pleural thickening, anatomy of the effusion, and detecting any endobronchial obstruction or mediastinal abnormality.[103]

Adequate nutritional support is necessary. Catabolism occurs related to chronic infection leading to further immunodeficiency and slow recovery. Hypoalbuminaemia is associated with poor outcome from pleural infection but this may be related to its negative acute phase response.

NEW DEVELOPMENTS

Serum mesothelin

Mesothelin is a 40 kDa mesothelial cell glycoprotein. In a blinded controlled study 84% of histologically confirmed mesothelioma patients (n = 44) had increased soluble mesothelin related protein levels compared with 2% of patients with other cancers or inflammatory pleural diseases (n = 160) and none of the healthy controls (n = 68).[104] None of the 33 asbestos exposed subjects with normal soluble mesothelin related concentrations developed mesothelioma over eight years.

Transforming growth factor β

Transforming growth factor β is a fibrogenic cytokine that is also anti-inflammatory. It does not stimulate pleural interlukin 8 release from mesothelial cells but increases collagen deposition, is superior to talc in animal models, and does not provoke an inflammatory response unlike other agents.[105 106]

Vascular endothelial growth factor

Vascular endothelial growth factor is a potent inducer of microvascular permeability. Intrapleural vascular endothelial growth factor levels are significantly up-regulated in malignancy.[48] Alternative strategies include trying to switch off vascular endothelial growth factor signalling and its downstream pathways.[107]

RAPID assessment

After post hoc analysis of the MIST trial data, further risk stratification is possible in assessing prognosis in pleural infection. The presence of five specific patient factors, at presentation, were associated with a worse outcome[108]: renal function (urea >7 mmol/l); age (>65 years), protein (serum albumin <25 g/l); inpatient (hospital acquired empyema); diastolic blood pressure (<70 mm Hg).

These parameters, may therefore, aid clinical decision making. However, this will obviously need to be validated prospectively first before it can be used as a clinical tool.

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IMAGES IN MEDICINE

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Branch retinal artery occlusion during coronary angiography

A 61 year old woman with asymptomatic aortic stenosis underwent elective left and right heart catheterisation for preoperative haemodynamic and angiographic assessment. Prior transthoracic echocardiogram had shown a peak pressure gradient across the aortic valve of 80 mm Hg. Transoesophageal echocardiography confirmed the presence of a bicuspid aortic valve with mild calcification. The left and right coronary arteries were angiographically normal. Repeated attempts at crossing the aortic valve with a conventional 6 French gauge pigtail catheter and subsequently a 6 French gauge Judkins right coronary artery catheter were unsuccessful.

During the procedure, the patient noted the abrupt onset of a left central scotoma that prompted referral for ophthalmological assessment. On examination the left visual acuity was reduced to 6/60. Fundal examination showed central retinal pallor (fig 1A) corresponding to the field defect with two white, non-refractile emboli in the branch retinal artery (fig 1B). This appearance is consistent with both calcific and platelet-fibrin emboli.

Retinal infarction is a rare complication of diagnostic coronary angiography although clinically inapparent cerebral infarction is recognised by magnetic resonance imaging in up to one fifth of patients with aortic stenosis in whom the valve is crossed by a cardiac catheter. The retinal circulation has a paucity of anastomoses and is thus very vulnerable to ischaemia. Although no single universally effective treatment exists, ocular massage, oral acetazolamide, anterior chamber paracentesis, and 95% oxygen with 5% carbon dioxide inhalation therapy can be tried in the acute phase to clear the obstruction before irreversible damage occurs. Branch retinal artery occlusions have a better prognosis than central retinal artery occlusions but a fixed visual field defect is usual. This case highlights the need for prompt recognition and urgent referral of any patient with visual symptoms during cardiac catheterisation, while once again questioning the safety of measurement of peak to peak gradient in assessment of the severity of aortic stenosis.

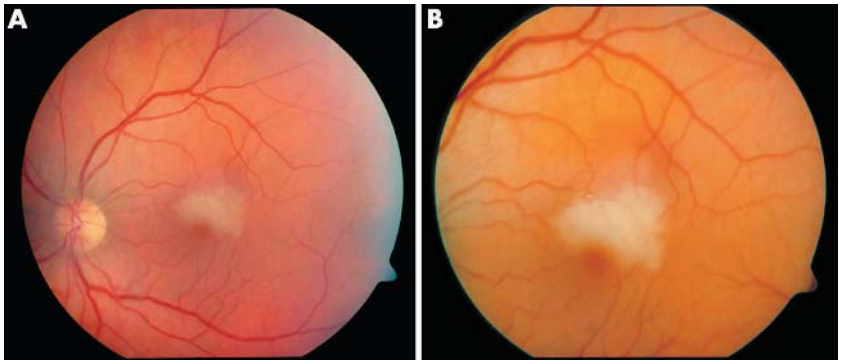

Figure 1 (A) Retinal photograph showing the left posterior pole with retinal whitening at the macula. (B) Magnification of the retinal photograph (A), showing two white, non-refractile emboli in a branch retinal artery subtending the infarcted area.

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