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BTS Pleural Disease Guideline 2010

British Thoracic Society
Pleural Disease Guideline Group

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Contact Details

Editorial Office
BMJ Publishing Group Ltd, BMA House, Tavistock Square London, WC1H 9JR, UK
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British Thoracic Society
17 Doughty Street
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T: **+44 (0)20 7831 8778**
F: **+44 (0)20 7831 8766**
E: **bts@brit-thoracic.org.uk**
http://www.brit-thoracic.org.uk/index.html

BTS Pleural Disease Guideline 2010

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Pleural Disease Guideline Group:
a sub-group of the British Thoracic Society
Standards of Care Committee

The BTS Pleural Disease Guideline is endorsed by:

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Royal College of Surgeons of England
Royal College of Physicians of Edinburgh
Royal College of Surgeons of Edinburgh
Royal College of Physicians and Surgeons of Glasgow
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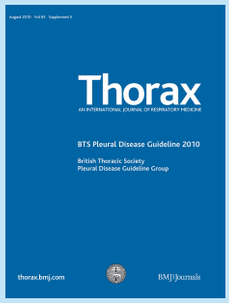

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Introduction and methods: British Thoracic Society pleural disease guideline 2010

Ingrid Du Rand,[1] Nick Maskell[2]

► Supplementary data are published online only. To view these files please visit the journal online (http://thorax.bmj.com).

[1]Selly Oak Hospital, UK
[2]Southmead Hospital, Bristol, UK

Correspondence to
Nick Maskell, Academic Respiratory Unit, Department of Clinical Sciences, Southmead Hospital University of Bristol, BS10 5NB;
nick.maskell@bristol.ac.uk

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CLINICAL CONTEXT

Pleural disease remains common, affecting over 3000 people per million population each year. They therefore represent a significant contribution to the workload of respiratory physicians. Pleural disease originates from a wide range of pathologies and a systematic approach to the investigation and management is therefore required. These guidelines attempt to summarise the available evidence to aid the healthcare professional in delivering good quality patient care.

NEED FOR GUIDELINE

The Standards of Care Committee of the British Thoracic Society (BTS) established a Pleural Disease Guideline Group in December 2007. The objective was to produce an evidence-based update of the last pleural disease guidelines published in 2003. It was recognised that, since the last guideline, a number of good quality primary research papers have been published and the guidelines needed to reflect these new data. In addition, there was a need to develop new sections on local anaesthetic thoracoscopy and thoracic ultrasound to reflect changes in clinical practice.

INTENDED USERS AND SCOPE OF THE GUIDELINE

This guideline is intended for use by all healthcare professionals who may be involved in pleural disease management. This will include doctors, nurses and other healthcare professionals.

AREAS COVERED BY THIS GUIDELINE

The guideline addresses the investigation and medical management of pleural disease in adults. This is divided into the following sections:

1. Investigation of a unilateral pleural effusion in adults.
2. Management of spontaneous pneumothorax.
3. Management of a malignant pleural effusion.
4. Management of pleural infection in adults.
5. Local anaesthetic thoracoscopy.
6. Chest drain insertion and thoracic ultrasound.

The six sections can be downloaded individually from the website. Key points are repeated within sections to give users a full review of the individual documents without the need to cross reference repeatedly. In addition, at the end of this section (Annex 1) there is a list of good areas for audit and future research.

AREAS NOT COVERED BY THIS GUIDELINE

The following areas fall outside the scope of this guideline:

1. Paediatric pleural disease
2. Detail on thoracic surgical techniques
3. Management of bilateral pleural effusions

METHODOLOGY

Establishment of guideline team

A Working Party was established with representation from a range of professionals with an interest in pleural disease together with a lay representative (see full list of Guideline Group members at the end of this section).

Scope of the guideline, PICOT questions and literature search

The guidelines are based upon the best available evidence. The methodology followed the criteria as set out by the Appraisal of Guidelines Research and Evaluation (AGREE) collaboration in the document the AGREE instrument available online at http://www.agreecollaboration.org/instrument/.

The scope and purpose of the guideline had been agreed and defined in consultation with all potential stakeholders representing the medical and nursing professions, patient groups, health management and industry (see full list of stakeholders at the end of this section).

Guideline members identified and formulated a set of key clinical questions in Population, Intervention, Comparison, Outcome, and Time (PICOT) format to inform the search strategies for the literature search.

The BTS commissioned the Centre for Reviews and Dissemination at the University of York to undertake a bespoke literature search using the search strategies shown in detail on the BTS website (http://www.brit-thoracic.org.uk). The following databases were searched: Ovid MEDLINE (from 1960 onwards) (including MEDLINE In Process), Ovid EMBASE, Cochrane Database of Systematic Reviews (CDRS), the Database of Abstracts of Reviews of Effects (DARE) and the Cochrane Central Register of Controlled Trials. The initial searches were done in June 2008 and revised in September 2009. Searches were limited to English and adult literature; 19 425 potential papers were identified by the search. (see online appendix 1).

The Guideline Committee agreed on the following criteria to select relevant abstracts for the guideline:

1. Studies that addressed the clinical question.
2. Appropriate study types used to produce the best evidence to answer the clinical question.
3. Non-English abstracts were not evaluated.
4. Abstracts were not rejected on the basis of the journal of publication, the country in which the research was done or published or the date of publication.

A total of 17 393 abstracts were rejected through the criteria outlined above and 2032 full papers were ordered for critical appraisal.

Critical appraisal of the literature

A further 591 full papers were rejected because they fell outside the area of focus and scope of the guideline. Formal critical appraisal to assess the clinical relevance and scientific rigor of 1441 papers was performed independently by at least two guideline reviewers using the Scottish Intercollegiate Guidelines Network (SIGN) critical appraisal checklists (see online appendix 2). The guideline reviewers identified an additional 148 papers during the period of guideline development which were added and critically appraised. The evidence in each study was graded using the SIGN formulated levels of evidence (table 1).

Considered judgement and grading of the evidence

Evidence tables were produced to review the body of evidence and inform the considered judgements and grading of recommendations. Where there was a lack of evidence, consensus statements were derived by incorporating a number of individual non-biased expert opinions from experts in the field.

The following were considered in grading of the recommendations:

1. The available volume of evidence.
2. The applicability of the obtained evidence for making recommendations for the defined target audience of this guideline.
3. How generalisable the obtained evidence was to the target population for the guideline.
4. A clear consistency in the evidence obtained to support recommendations.
5. The implications of recommendations on clinical practice in terms of recourses and skilled expertise.
6. In-depth cost-effectiveness analysis falls outside the scope of this guideline.

Recommendations were graded from A+ to D as indicated by the strength of the evidence as listed in table 2.

Drafting of the guideline

The Guideline Group produced a draft guideline following regular email consultations and meetings held in December 2007, June 2008, November 2008, February 2009 and May 2009. The draft guideline was presented at the Summer BTS meeting in June 2009 and circulated to all the stakeholders identified (see below) for consultation and review.

The revised draft guideline was submitted to the BTS Standards of Care Committee for review and published online for a month (in August 2009) to allow for BTS member and public consultation. All the feedback was reviewed and discussed by the Guideline Committee and incorporated into the revised draft guideline. The literature search was repeated by the Centre for Reviews and Dissemination and Centre for Health Economics at the University of York and additional evidence appraised and included in the final draft of the guideline.

Table 1 Revised grading system for recommendations in evidence-based guidelines

Grade	Evidence
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews or RCTs or RCTs with a high risk of bias
2++	High quality systematic reviews of case–control or cohort studies or high quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies—for example, case reports, case series
4	Expert opinion

Table 2 Grades of recommendations

Grade	Type of evidence
A	At least one meta-analysis, systematic review or randomised controlled trial (RCT) rated as 1++ and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3or 4; or Extrapolated evidence from studies rated as 2+
✓	Important practical points for which there is no—nor is there likely to be any—research evidence. The guideline committee wishes to emphasise these as Good Practice Points (GPP)

PLANNED REVIEW OF THE GUIDELINE

The guideline will be reviewed and updated in 4 years from publication.

GUIDELINE GROUP MEMBERSHIP

Guideline Group members: Dr Nick Maskell (Chair), Dr Nabeel Ali, Dr George Antunes, Dr Anthony Arnold, Professor Robert Davies, Dr Chris Davies, Dr Fergus Gleeson, Dr John Harvey, Dr Diane Laws, Professor YC Gary Lee, Dr Edmund Neville, Dr Gerrard Phillips, Dr Richard Teoh, Dr Naj Rahman, Dr Helen Davies, Dr Tom Havelock, Dr Clare Hooper, Dr Andrew MacDuff, Dr Mark Roberts.

Dr Edmund Neville represented the Royal College of Physicians, London. Dr Fergus Gleeson represented the Royal College of Radiologists. Thoracic surgical representatives: Mr Richard Berrisford, Mr Jim McGuigan (representing the Royal College of Surgeons), Mr Richard Page (representing the Royal College of Surgeons of Edinburgh).

Dr D L Evans (member of the BTS Standards of Care Committee) provided lay input during consultation phases of the production of the guideline.

STAKEHOLDER ORGANISATIONS

The following organisations were identified as stakeholders and given the opportunity to comment on the draft documents during the consultation period: Royal College of Physicians, London; Royal College of Surgeons of England; Royal College of Physicians of Edinburgh; Royal College of Surgeons of Edinburgh; Royal College of Radiologists; Royal College of Anaesthetists; Royal College of General Practitioners; Royal College of Nursing; Royal College of Obstetricians and Gynaecologists; Royal College of Pathologists; Joint Royal Colleges Ambulance Liaison Committee; College of Emergency Medicine; Society for Acute Medicine; Association for Palliative Medicine of GB and Ireland; British Geriatrics Society; Association for Clinical Biochemistry; Association of Medical Microbiologists; British Society for Immunology; British Society of Clinical Cytology; British Society for Rheumatology; Society for Cardiothoracic Surgery in Great Britain and Ireland.

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Competing interests No member of the Guideline Group is aware of any competing interests.

Provenance and peer review The draft guideline was available for online public consultation (July/August 2009) and presented to the BTS Winter Meeting (December 2009). Feedback was invited from a range of stakeholder institutions (see Introduction). The draft guideline was reviewed by the BTS Standards of Care Committee (September 2009).

ANNEX 1 FUTURE RESEARCH DIRECTIONS AND AUDITS

Possible future areas that deserve further research:

1. Randomised controlled trial looking at the efficacy of talc poudrage versus talc slurry in controlling symptomatic malignant pleural effusions.
2. Optimal timing of drain removal post pleurodesis.
3. Thoracoscopic pleural biopsies — optimal size, number and distribution.
4. A large multi centre RCT comparing observation versus aspiration versus chest tube drainage in primary pneumothorax using patient centered outcomes.
5. Role of ambulatory catheters in treatment and management of primary and secondary pneumothorax.
6. Comparison of the efficacy and patient satisfaction between chest tube drainage with talc slurry and indwelling pleural catheter placement as first line treatment of malignant pleural effusions.
7. Safety of using indwelling pleural catheters in patients undergoing/about to undergo chemotherapy.
8. Value of serum and pleural fluid biomarkers in distinguishing underlying cause of pleural disease reducing the need for invasive procedures.
9. Studies on the detection of pneumothorax - comparing the newer ward-based digital technology with standard radiography.
10. Role of pleural irrigation in cases of pleural infection requiring simple chest tube drainage.

Possible pleural audits:

1. Consent documentation for chest drain insertion.
2. Chest drain iatrogenic infection rates.
3. Chest tube 'fall out' rate.
4. Availability of bedside ultrasound for pleural procedures.
5. Length of in-patient stay for new undiagnosed pleural effusions.
6. Pleurodesis success rates.
7. Trust adherence to the management algorithm for pneumothorax.
8. Documentation of discharge advice for patients with pneumothorax.
9. Local sensitivity of pleural fluid cytology
10. Documentation of pleural fluid pH in cases of pleural infection and use of heparinized syringes.
11. Appropriate antibiotic use/duration in cases of pleural infection. Are blood cultures always taken.
12. Diagnostic yields and complication rates of local anaesthetic thoracoscopy.
13. Is DVT prophylaxis prescribed (where no CI) for all cases of pleural infection and malignancy requiring a chest drain.
14. Size of chest tube used in cases of pneumothorax and length of time before surgical referral made.
15. CT/US guided pleural biopsy diagnostic sensitivity for malignancy.

Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline 2010

Clare Hooper,[1] Y C Gary Lee,[2] Nick Maskell,[3] on behalf of the BTS Pleural Guideline Group

[1]Southmead Hospital, Bristol, UK
[2]Lung Institute of Western Australia, University Dept Med, Perth, Western Australia, Australia
[3]Department of Clinical Sciences, Southmead Hospital, University of Bristol, Bristol, UK

Correspondence to
Nick Maskell, Academic Respiratory Unit, Department of Clinical Sciences, Southmead Hospital, University of Bristol, BS10 5NB;
nick.maskell@bristol.ac.uk

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INTRODUCTION

Pleural effusions are a common medical problem with more than 50 recognised causes including disease local to the pleura or underlying lung, systemic conditions, organ dysfunction and drugs.[1]

Pleural effusions occur as a result of increased fluid formation and/or reduced fluid resorption. The precise pathophysiology of fluid accumulation varies according to underlying aetiologies. As the differential diagnosis for a unilateral pleural effusion is wide, a systematic approach to investigation is necessary. The aim is to establish a diagnosis swiftly while minimising unnecessary invasive investigations and facilitating treatment, avoiding the need for repeated therapeutic aspirations when possible.

Since the 2003 guideline, several clinically relevant studies have been published, allowing new recommendations regarding image guidance of pleural procedures with clear benefits to patient comfort and safety, optimum pleural fluid sampling and processing and the particular value of thoracoscopic pleural biopsies. This guideline also includes a review of recent evidence for the use of new biomarkers including N-terminal pro-brain natriuretic peptide (NT-proBNP), mesothelin and surrogate markers of tuberculous pleuritis.

CLINICAL ASSESSMENT AND HISTORY

- **Aspiration should not be performed for bilateral effusions in a clinical setting strongly suggestive of a transudate unless there are atypical features or they fail to respond to therapy. (✓)**
- **An accurate drug history should be taken during clinical assessment. (✓)**

The history and physical examination of a patient with a pleural effusion may guide the clinician as to whether the effusion is a transudate or an exudate. This critical distinction narrows the differential diagnosis and directs further investigation.

Clinical assessment alone is often capable of identifying transudative effusions. Therefore, in an appropriate clinical setting such as left ventricular failure with a confirmatory chest x-ray, such effusions do not need to be sampled unless there are atypical features or they fail to respond to treatment.

Approximately 75% of patients with pulmonary embolism and pleural effusion have a history of pleuritic pain. These effusions tend to occupy less than one-third of the hemithorax and the dyspnoea is often out of proportion to the size of the effusion.[2 3] As tests on the pleural fluid are unhelpful in diagnosing pulmonary embolism, a high index of suspicion is required to avoid missing the diagnosis.

The patient's drug history is also important. Although uncommon, a number of medications have been reported to cause exudative pleural effusions (box 1). Useful resources for more detailed information include the *British National Formulary* and the web site http://www.pneumotox.com/.

An occupational history including details about known or suspected asbestos exposure and potential secondary exposure via parents or spouses should be documented. An algorithm for the iinvestigation of a unilateral pleural effusion is shown in figure 1.

INITIAL DIAGNOSTIC IMAGING

Plain radiography

- **Posteroanterior (PA) chest x-rays should be performed in the assessment of suspected pleural effusion. (✓)**

The plain chest radiographic features of pleural effusion are usually characteristic. The posteroanterior (PA) chest x-ray is abnormal in the presence of about 200 ml of pleural fluid. However, only 50 ml of pleural fluid can produce detectable posterior costophrenic angle blunting on a lateral chest x-ray.[4]

In the intensive care setting, most chest x-rays are performed as AP supine examinations, resulting in free pleural fluid lying posteriorly in the dependent portion of the chest. Consequently, effusions are seen as an increase in hemithorax opacity with preserved vascular shadows on the supine x-ray. Other signs include the loss of the sharp silhouette of the ipsilateral hemidiaphragm and fluid tracking

Box 1 Commonly prescribed drugs known to cause pleural effusions (over 100 cases reported globally)

- Methotrexate
- Amiodarone
- Phenytoin
- Nitrofurantoin
- β-blockers

Source: http://www.pneumotox.com (2009)

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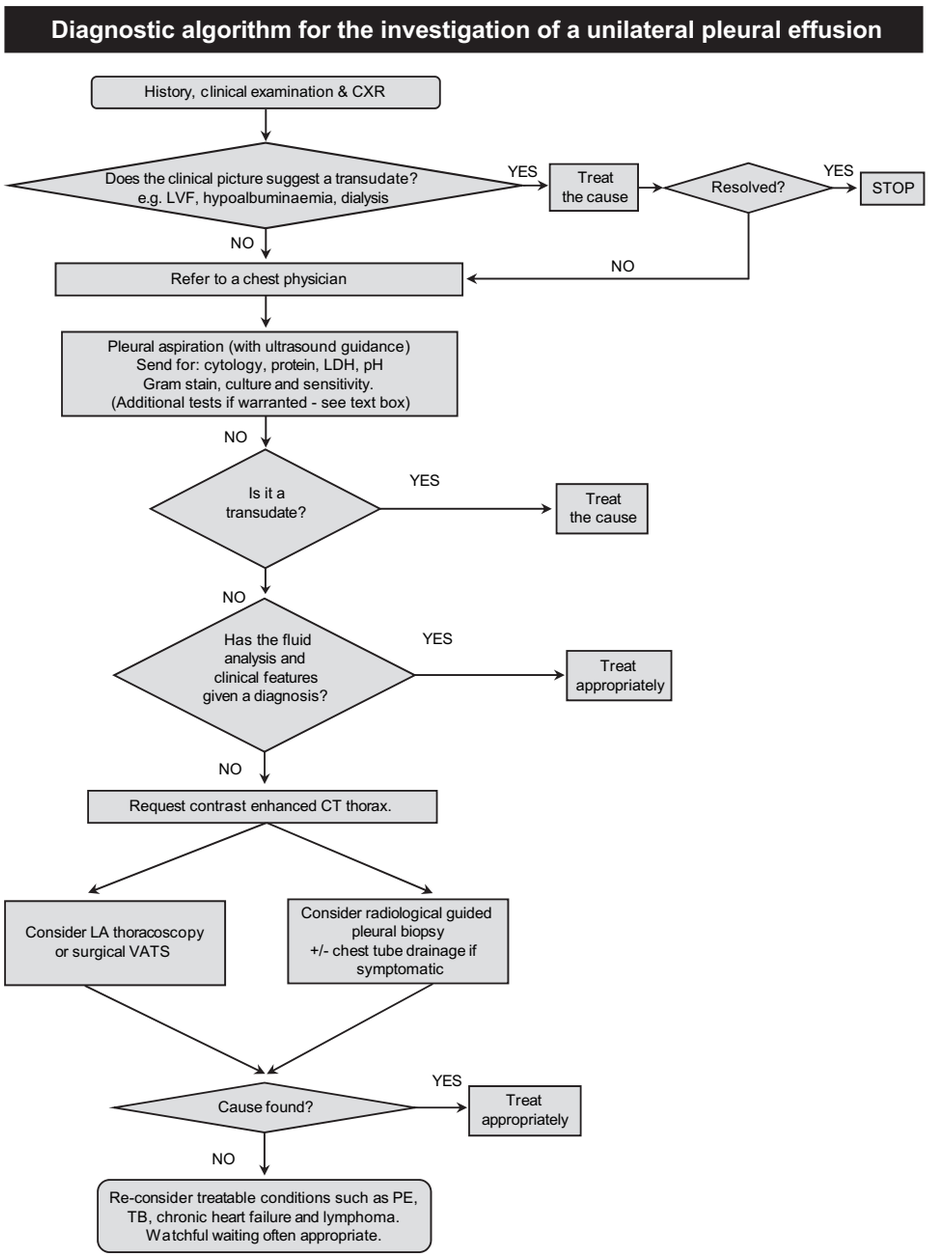

Figure 1 Diagnostic algorithm for the investigation of a unilateral pleural effusion.

down into the oblique or horizontal fissures resulting in apparent fissural thickening. The volume of pleural fluid is commonly underestimated on a supine chest x-ray and 'normal' appearances do not exclude the presence of an effusion.[5]

Subpulmonic effusions occur when pleural fluid accumulates between the diaphragmatic surface of the lung and the diaphragm. They are often transudates, can be difficult to diagnose on the PA film and may require an ultrasound scan. The PA film will often show a lateral peaking of an apparently raised hemidiaphragm which has a steep lateral slope with a gradual medial slope (see figure 2). The lateral x-ray may have a flat appearance of the posterior aspect of the hemidiaphragm with a steep downward slope at the major fissure.[6]

Ultrasound

- **Bedside ultrasound guidance significantly increases the likelihood of successful pleural fluid aspiration and reduces the risk of organ puncture. (B)**
- **Ultrasound detects pleural fluid septations with greater sensitivity than CT. (C)**

Ultrasound guidance improves the rate of successful pleural aspiration. Several studies have shown that fluid can be successfully obtained using ultrasound in up to 88% of patients after a failed clinical and plain chest x-ray-guided attempt.[7–9]

Ultrasound guidance reduces the incidence of iatrogenic pneumothorax following thoracentesis and several studies have shown this effect to be independent of the size of the effusion.[10 11] This benefit appears to be lost when the 'X marks the spot' method is employed, presumably due to differences in patient positioning between the ultrasound and the procedure.[12]

Clinical judgement with review of the chest x-ray was compared with ultrasonography in planning the diagnostic aspiration site in a prospective study including 255 clinician assessments of 67 patients.[4] The sensitivity and specificity of clinical judgement compared with the gold standard of ultrasound was 76.6% and 60.3%, respectively. Ultrasound increased

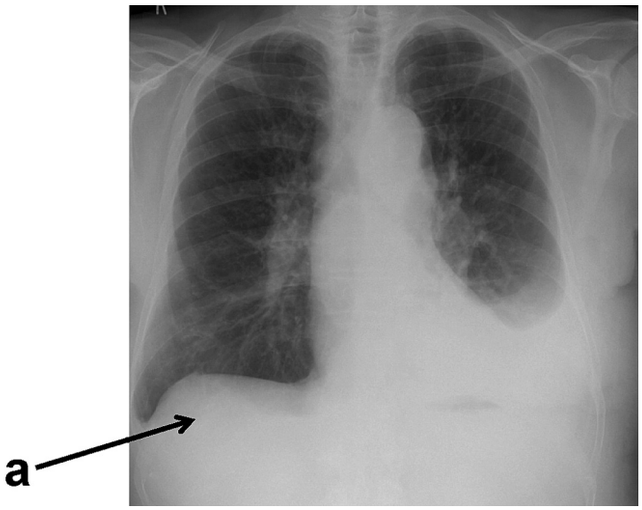

Figure 2 Chest x-ray showing a moderate left pleural effusion and subpulmonic effusion on the right (a). Note the lateral peaking of the right hemidiaphragm. Reproduced with permission from Professor David Milne, Auckland University.

the number of accurate sites by 26%; 15% of clinically determined sites would have resulted in the puncture of liver, spleen or lung and, although there was increasing risk with small or loculated effusions, 60% of potential organ punctures occurred in radiologically large or moderate effusions.

Ultrasound is superior to plain radiography in diagnosing and quantifying pleural effusions and distinguishes pleural fluid from thickening with high specificity, particularly when colour Doppler is employed.[13–16] It is particularly useful in the diagnosis of small effusions or in recumbent patients (eg, ventilated and critically ill) due to the low sensitivity of plain radiography in these situations.

The diagnostic role of thoracic ultrasound in the early investigation of pleural effusions extends beyond the identification and safe aspiration of fluid.

Ultrasound detects septations within pleural fluid with greater sensitivity than CT scanning.[17] A septated appearance may be observed in malignant effusions or pleural infection and occurs with similar frequency in the two diagnoses.[18]

Ultrasound positively identifies exudative effusions when pleural fluid is complex, septated or echogenic, although simple (anechoic) effusions can be exudates or transudates.[19]

Ultrasound features can distinguish malignant from benign effusions. Qureshi *et al* demonstrated 95% specificity for a malignant diagnosis, 95% for parietal pleural thickening >1 cm, 100% for visceral pleural thickening, 95% for diaphragmatic thickening >7 mm and 100% for diaphragmatic nodules as visualised on ultrasound examination.[20] Overall sensitivity of ultrasound in the differentiation of malignant from benign effusions was 79% (95% CI 61% to 91%) and specificity of 100% (95% CI 82% to 100%), with specificity comparing favourably with CT scanning (89%).

PLEURAL ASPIRATION

- **A diagnostic pleural fluid sample should be aspirated with a fine-bore (21G) needle and a 50 ml syringe. (✓)**
- **Bedside ultrasound guidance improves the success rate and reduces complications (including pneumothorax) and is therefore recommended for diagnostic aspirations. (B)**
- **Pleural fluid should always be sent for protein, lactate dehydrogenase, Gram stain, cytology and microbiological culture. (C)**

This is the primary means of evaluating pleural fluid and its findings are used to guide further investigation.

Pleural ultrasound should be used at the bedside to select a pleural aspiration site with safety. Ultrasound increases the chances of successful aspiration and minimises the need for repeated attempts.[21] Direct ultrasound-guided aspiration or ultrasound at the bedside immediately before the procedure is preferable to the 'X marks the spot' approach. A lateral site is preferred, provided that adequate fluid is demonstrated here on ultrasound as the risk of intercostal vessel trauma increases with more posterior or medial punctures (see figure 3).

Patient consent and further technical details of pleural aspiration are covered in the guideline on pleural procedures. Table 1 shows sample collection guidance for specific pleural fluid tests.

A green needle (21G) and 50 ml syringe are adequate for diagnostic pleural aspirations. If there is diagnostic suspicion of pleural infection and a pleural fluid pH is to be measured, aspirated fluid should immediately be drawn into a heparinised blood gas syringe which should then be capped while awaiting analysis to avoid exposure of the fluid to the air. The remaining sample should be divided between sample pots for microbiological (5 ml), biochemical (2–5 ml) and cytological (remaining sample which should be 20–40 ml) analysis. Microscopic examination of Gram-stained pleural fluid sediment is necessary for all pleural fluid samples. If infection is suspected, some of the pleural fluid should be sent in blood culture bottles which increases diagnostic accuracy, particularly for anaerobic organisms.[22]

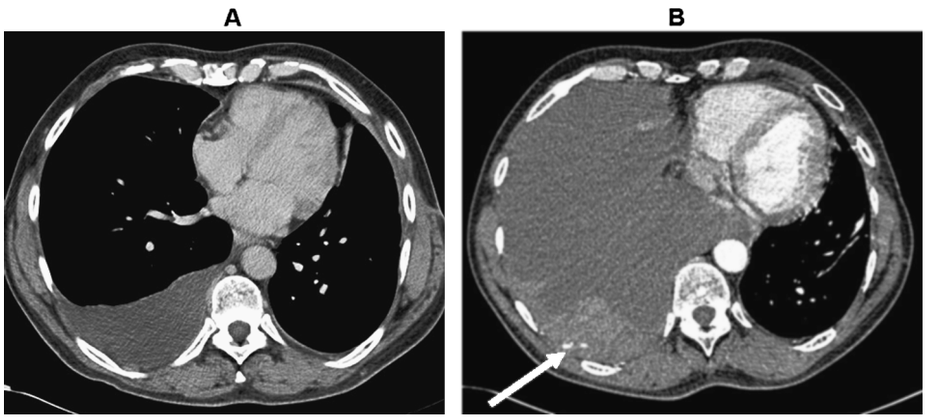

Figure 3 CT scan (A) before and (B) 2 days later after a pleural aspiration with inappropriate medial approach and intercostal artery puncture with resultant haemothorax requiring surgical intervention. Note the active bleeding indicated by the arrow.

Table 1 Pleural fluid tests and sample collection guidance

Test	Notes
Recommended tests for all sampled pleural effusions	
Biochemistry: LDH and protein	2–5 ml in plain container or serum blood collection tube depending on local policy. Blood should be sent simultaneously to biochemistry for total protein and LDH so that Light's criteria can be applied
Microscopy and culture (MC and S)	5 ml in plain container. If pleural infection is particularly suspected, a further 5 ml in both anaerobic and aerobic blood culture bottles should be sent
Cytological examination and differential cell count	Maximum volume from remaining available sample in a plain universal container. Refrigerate if delay in processing anticipated (eg, out of hours)
Other tests sent only in selected cases as described in the text	
pH	In non-purulent effusions when pleural infection is suspected. 0.5–1 ml drawn up into a heparinised blood gas syringe immediately after aspiration. The syringe should be capped to avoid exposure to air. Processed using a ward arterial blood gas machine
Glucose	Occasionally useful in diagnosis of rheumatoid effusion. 1–2 ml in fluoride oxalate tube sent to biochemistry
Acid-fast bacilli and TB culture	When there is clinical suspicion of TB pleuritis. Request with MC and S. 5 ml sample in plain container
Triglycerides and cholesterol	To distinguish chylothorax from pseudochylothorax in milky effusions. Can usually be requested with routine biochemistry (LDH, protein) using the same sample
Amylase	Occasionally useful in suspected pancreatitis-related effusion. Can usually be requested with routine biochemistry
Haematocrit	Diagnosis of haemothorax. 1–2 ml sample in EDTA container sent to haematology

LDH, lactate dehydrogenase; PH, pulmonary hypertension; TB, tuberculosis

There is conflicting evidence regarding the optimum volume of pleural fluid for diagnosis of malignancy; sensitivity depends on the cellularity of the sample and processing technique as well as volume submitted.[23 24] It is sensible to send as large a volume as possible from the 50–60 ml sample obtained following diagnostic aspiration as other tests only require small volumes. At room temperature the sample for cytology should be sent to the laboratory as quickly as possible but, if a delay is anticipated, the specimen can be refrigerated at 4°C for up to 14 days with no deterioration in the diagnostic yield for malignancy (table 1).[25]

Appearance

- **The appearance of the pleural fluid and any odour should be recorded. (✓)**
- **A pleural fluid haematocrit is helpful in the diagnosis of haemothorax. (✓)**

Table 2 summarises the appearance of pleural effusions due to specific causes. Fluid may appear serous, blood-tinged, frankly bloody or purulent. Centrifuging turbid or milky pleural fluid will distinguish between empyema and lipid effusions. If the supernatant is clear, the turbid fluid was due to cell debris and empyema is likely while, if it is still turbid, chylothorax or pseudochylothorax are likely.[26] The unpleasant smell of anaerobic infection may guide antibiotic choices and the smell of ammonia suggests urinothorax.

Grossly bloody pleural fluid is usually due to malignancy, pulmonary embolus with infarction, trauma, benign asbestos pleural effusions or post-cardiac injury syndrome.[27 28]

A haemothorax can be distinguished from other blood-stained effusions by performing a haematocrit on the pleural fluid. A pleural fluid haematocrit >50% of the patient's peripheral blood haematocrit is diagnostic of a haemothorax.[29]

Table 2 Diagnostically useful pleural fluid characteristics

Fluid	Suspected disease
Putrid odour	Anaerobic empyema
Food particles	Oesophageal rupture
Bile stained	Cholothorax (biliary fistula)
Milky	Chylothorax/pseudochylothorax
'Anchovy sauce' like fluid	Ruptured amoebic abscess

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 is >0.5
- Pleural fluid lactate dehydrogenase (LDH) divided by serum LDH is >0.6
- Pleural fluid LDH >2/3 the upper limits of laboratory normal value for serum LDH.

Differentiating between a pleural fluid exudate and transudate

- **Light's criteria should be used to distinguish between a pleural fluid exudate and transudate (box 2). (B)**
- **In order to apply Light's criteria, the total protein and lactate dehydrogenase (LDH) should be measured in both blood and pleural fluid. (B)**

Categorisation of pleural effusions into transudates and exudates is an important early step in narrowing the differential diagnosis and directing subsequent investigations and management (see boxes 3 and 4).

Classically, pleural fluid protein >30 g/l has indicated an exudate and <30 g/l a transudate. This classification is not accurate when serum protein is abnormal or when the pleural fluid protein is close to 30 g/l and, as this is very common, the application of Light's criteria is always recommended.[30]

A considerable number of other biochemical markers have been compared with Light's criteria but the latter, with a diagnostic

Box 3 Causes of pleural transudates

Very common causes
- Left ventricular failure
- Liver cirrhosis

Less common causes
- Hypoalbuminaemia
- Peritoneal dialysis
- Hypothyroidism
- Nephrotic syndrome
- Mitral stenosis

Rare causes
- Constrictive pericarditis
- Urinothorax
- Meigs' syndrome

Box 4 Causes of pleural exudates

Common causes
- Malignancy
- Parapneumonic effusions
- Tuberculosis

Less common causes
- Pulmonary embolism
- Rheumatoid arthritis and other autoimmune pleuritis
- Benign asbestos effusion
- Pancreatitis
- Post-myocardial infarction
- Post-coronary artery bypass graft

Rare causes
- Yellow nail syndrome (and other lymphatic disorders eg, lymphangioleiomyomatosis)
- Drugs (see table 2)
- Fungal infections

Box 5 Causes of lymphocytic pleural effusions (ie, lymphocytes account for >50% of nucleated cells)

- Malignancy (including metastatic adenocarcinoma and mesothelioma)
- Tuberculosis
- Lymphoma
- Cardiac failure
- Post-coronary artery bypass graft
- Rheumatoid effusion
- Chylothorax
- Uraemic pleuritis
- Sarcoidosis
- Yellow nail syndrome

accuracy of 93–96%, remains a robust method.[31 32] This discriminatory accuracy is unlikely to be surpassed as the 'gold standard' for comparison in clinical diagnosis which itself carries an error rate.

In congestive cardiac failure, diuretic therapy increases the concentration of protein, lactate dehydrogenase (LDH) and lipids in pleural fluid and, in this context, Light's criteria are recognised to misclassify a significant proportion of effusions as exudates.[33 34]

Although the use of continuous likelihood ratios rather than a dichotomous division of transudates versus exudates has been proposed, particularly to overcome loss of accuracy of Light's criteria when pleural protein and LDH levels are close to cut-off values, there is probably little value in this cumbersome statistical method beyond careful interpretation of test results in the light of clinical judgement.[35]

N-terminal pro-brain natriuretic peptide (NT-proBNP)

NT-proBNP is a sensitive marker of both systolic and diastolic cardiac failure. Levels in blood and pleural fluid correlate closely and measurement of both has been shown in several series to be effective in discriminating transudates associated with congestive heart failure from other transudative or exudative causes.[36–39] The cut-off value of these studies, however, varied widely from 600 to 4000 pg/ml (with 1500 pg/ml being most commonly used), and most studies excluded patients with more than one possible aetiology for their effusion. NT-proBNP has been shown to correctly diagnose congestive heart failure as a cause of most effusions that have been misclassified as exudates by Light's criteria. Use of this test may therefore avoid repeated invasive investigations in patients where there is a strong clinical suspicion of cardiac failure.[40–42] As results with pleural fluid and blood are comparable, applying the test to blood alone is sufficient (see evidence table A available on the BTS website at www.brit-thoracic.org.uk).

Evidence for the use of measuring BNP (also known as C-terminal BNP, the active peptide from which NT-proBNP is cleaved) is relatively scarce to date.

Pleural fluid differential cell counts

- **Pleural fluid cell proportions are helpful in narrowing the differential diagnosis but none are disease-specific. (C)**
- **Any long-standing pleural effusion tends to become populated by lymphocytes. Pleural malignancy, cardiac failure and tuberculosis are common specific causes of lymphocyte-predominant effusions. (C)**

If the pleural fluid differential cell count shows a predominant lymphocytosis (>50% cells are lymphocytes), the most likely diagnoses worldwide are malignancy and tuberculosis (TB).[43] Cardiac failure is also a common cause of a lymphocytic effusion. Very high lymphocyte proportions (>80%) occur most frequently in TB, lymphoma, chronic rheumatoid pleurisy, sarcoidosis and late post-coronary artery bypass grafting (CABG) effusions (see box 5).[44]

Neutrophil-predominant pleural effusions are associated with acute processes. They occur in parapneumonic effusions, pulmonary embolism, acute TB and benign asbestos pleural effusions.[28 45]

Pleural effusions in which ≥10% of cells are eosinophils are defined as eosinophilic.[46] The most common cause of pleural fluid eosinophilia is air or blood in the pleural space.[47] Pleural eosinophilia is a relatively non-specific finding as it can occur in parapneumonic effusions, drug-induced pleurisy, benign asbestos pleural effusions, Churg–Strauss syndrome, lymphoma, pulmonary infarction and parasitic disease.[48 49] Malignancy is also a common cause; a malignant diagnosis was made in 37% of 60 eosinophilic effusions in one series.[46]

pH

- **In non-purulent effusions, when pleural infection is suspected, pleural fluid pH should be measured providing that appropriate collection technique can be observed and a blood gas analyser is available. (B)**
- **Inclusion of air or local anaesthetic in samples may significantly alter the pH results and should be avoided. (B)**
- **In a parapneumonic effusion, a pH of <7.2 indicates the need for tube drainage. (B)**

Pleural fluid acidosis (pH <7.30) occurs in malignant effusions, complicated pleural infection, connective tissue diseases (particularly rheumatoid arthritis), tuberculous pleural effusions and oesophageal rupture and, in isolation, it does not distinguish between these causes.[50]

Pleural fluid acidosis reflects an increase in lactic acid and carbon dioxide production due to locally increased metabolic activity as well as a fall in hydrogen ion flux across abnormal pleural membranes. Increased consumption of glucose without replacement in the same conditions means that pleural fluid often has both a low pH and low glucose concentration.[51]

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In malignant pleural effusions low pH has been associated with shorter survival, more extensive disease and a lower chance of successful pleurodesis.[52] A meta-analysis including 417 patients with malignant pleural effusions found that a pleural pH <7.28 was associated with a median survival of 2.5 months and a 3-month survival of 38.9% (95% CI 31.1% to 46.8%) compared with a median survival of 4.3 months and 3-month survival of 61.6% (95% CI 55.7% to 67.4%) if the pH was >7.28.[53]

In clinical practice, the most important use for pleural fluid pH is aiding the decision to treat pleural infection with tube drainage. A meta-analysis of studies examining pleural pH and the need for chest tube drainage or surgery in patients with a parapneumonic effusion found that a pH <7.2 was the most specific discriminator of complicated pleural infection.[54] This is covered in detail in the pleural infection guideline.

In loculated parapneumonic effusions, fluid pH has been shown to vary significantly between locules so that a pH >7.2 in a patient with other clinical indicators of complicated pleural infection should be viewed with caution.[55]

The collection and analysis technique can have a clinically significant impact on pleural fluid pH results. A prospective study found that exposure of fluid to air in the syringe increased the measured pleural fluid pH by ≥0.05 in 71% of samples and inclusion of 0.2 ml local anaesthetic produced a mean reduction in pH of 0.15 (95% CI 0.13 to 0.18).[56] Pleural fluid should therefore be collected and transported without exposure to atmospheric air and local anaesthetic avoided for diagnostic aspirations where the pH will be used to guide management. Pleural pH does not change significantly if processing is delayed for up to an hour at room temperature. An arterial blood gas analyser should be used.[57] In routine clinical practice it is often difficult to adhere to these collection requirements and, when they cannot be achieved, overall clinical assessment may be preferable to reliance on a suboptimal pleural fluid pH result.

Glucose

In the absence of pleural pathology, glucose diffuses freely across the pleural membrane and the pleural fluid glucose concentration is equivalent to blood.[1]

A low pleural fluid glucose level (<3.4 mmol/l) may be found in complicated parapneumonic effusions, empyema, rheumatoid pleuritis and pleural effusions associated with TB, malignancy and oesophageal rupture.[1] The most common causes of a very low pleural fluid glucose level (<1.6 mmol/l) are rheumatoid arthritis and empyema.[58 59]

Although glucose is usually low in pleural infection and correlates with pleural fluid pH values, it is a significantly less accurate indicator for chest tube drainage than pH.[54]

When pleural fluid glucose is measured, the sample should be sent in a fluoride oxalate tube.

Amylase

- **Routine measurements of pleural fluid amylase or its isoenzymes are not warranted. It can, however, be useful in suspected cases of oesophageal rupture or effusions associated with pancreatic diseases. (C)**

Pleural fluid amylase levels are elevated if they are higher than the upper limit of normal for serum or the pleural fluid/serum ratio is >1.0.[60] This suggests acute pancreatitis, pancreatic pseudocyst, rupture of the oesophagus, ruptured ectopic pregnancy or pleural malignancy (especially adenocarcinoma).[61 62] Approximately 10% of malignant effusions have raised pleural fluid amylase levels,[63] although there is probably no role for pleural amylase estimation in the routine investigation of malignant effusions.[64]

Isoenzyme analysis can be useful but is not readily available in many laboratories. Elevation of salivary amylase suggests oesophageal rupture or malignancy.[61 62] Pleural effusions associated with pancreatic disease usually contain pancreatic amylase.[61] The incidence of pleural effusion with acute pancreatitis exceeds 50%. Patients with acute pancreatitis and a pleural effusion tend to have more severe disease and a higher likelihood of subsequently developing a pseudocyst than those without effusions.[65] If oesophageal rupture is entertained as a differential diagnosis, urgent more specific investigation by contrast radiography or endoscopy is indicated.

There are few data regarding the measurement of pleural fluid lipase, although case reports of pleural effusions secondary to pancreatitis have described its elevation alongside amylase.[66]

CYTOLOGY

- **Malignant effusions can be diagnosed by pleural fluid cytology in about 60% of cases. (B)**
- **The yield from sending more than two specimens (taken on different occasions) is very low and should be avoided. (B)**
- **Immunocytochemistry should be used to differentiate between malignant cell types and can be very important in guiding oncological therapy. (C)**

If malignancy is suspected, cytological examination of the pleural fluid is a quick and minimally invasive way to obtain a diagnosis. Series examining the diagnostic rate for malignancy of pleural cytology have reported a mean sensitivity of about 60% (range 40–87%).[67–70] The yield from sending more than two specimens of pleural fluid taken on different occasions is low. One study found a yield of 65% from the first specimen, a further 27% from the second specimen and only 5% from the third.[70] The diagnostic yield for malignancy depends on sample preparation, the experience of the cytologist and on tumour type. The diagnostic rate is higher for adenocarcinoma than for mesothelioma, squamous cell carcinoma, lymphoma and sarcoma.

Swiderek *et al* found that submission of a 60 ml pleural fluid sample produced a significantly better sensitivity for the diagnosis of malignancy than 10 ml, but previous studies have shown that sending volumes >50 ml did not improve the diagnostic yield.[23 24] The evidence for sending large volumes of pleural fluid is not strong enough to justify the increased risk of complications associated with the use of a venflon and three-way tap for initial diagnostic aspiration. As much fluid as possible should be sent for cytology from the available diagnostic sample (likely to be 20–40 ml) and, when the initial result is negative but malignancy is suspected, the sending of a higher volume sample following a second aspiration should be considered. If the initial aspiration is both therapeutic and diagnostic, ≥60 ml should be sent for cytological examination.

Pleural fluid should be sent in a plain container which allows the cellular portion to separate, forming a fibrinous 'clot' which may enmesh malignant cells. These can then undergo histological examination and are reported with the fluid cytology. Some departments, however, prefer the use of bottles containing sodium citrate to keep the cells in free suspension. No other anticoagulants or preservatives should be used as they may interfere with cellular adherence to slides and immunocytochemistry.

Table 3 Reporting of pleural fluid cytology results

Report	Interpretation
Inadequate	No mesothelial cells or only degenerate cells present
No malignant cells seen	Adequate sample without evidence of malignancy (does not exclude malignancy)
Atypical cells	May be of inflammatory or malignant origin. Sending a further sample may be helpful
Suspicious for malignancy	Occasional cells with malignant features but not definitively malignant
Malignant	Unequivocal malignant cells present which require typing by immunocytochemistry

The yield for malignancy increases if both cell blocks (which are formed by centrifuging the sample and extracting the solid cellular portion) and smears are prepared from pleural fluid samples.[71]

Table 3 provides an interpretation of common pleural fluid cytology reports seen in clinical practice.

Once malignancy has been confirmed morphologically, immunocytochemistry should be used to differentiate between different malignant cell types. This can be performed on a cytology sample, cell block or a clot.[72] There is particularly extensive morphological overlap between malignant mesothelioma and metastatic adenocarcinoma cells and immunocytochemistry can assist in their differentiation. However, whenever possible, pleural tissue should be obtained to confirm a diagnosis of malignant mesothelioma.

If lymphoma is suspected on morphological examination, ideally a sample should be submitted for flow cytometry for further typing, but immunocytochemistry can be used if this is unavailable (table 3).[73]

TUMOUR MARKERS

- **Pleural fluid and serum tumour markers do not currently have a role in the routine investigation of pleural effusions. (C)**

At a cut-off level that achieves 100% specificity for the diagnosis of malignancy, a panel of pleural fluid tumour markers including CEA, CA-125, CA 15-3 and CYFRA has been shown to reach a combined sensitivity of only 54%, such that a negative result cannot be used to support a conservative approach to monitoring and investigation.[74]

Mesothelin, however, has been shown to have more promising diagnostic characteristics (see evidence table B available on the BTS website at www.brit-thoracic.org.uk).

Mesothelin

Mesothelin is a glycoprotein tumour marker that is present at higher mean concentrations in the blood and pleural fluid of patients with malignant mesothelioma than in patients with other causes of pleural effusion.[75 76] Studies examining mesothelin levels in serum and/or pleural fluid have demonstrated a sensitivity of 48–84% and specificity of 70–100% for the diagnosis of mesothelioma.[75–80] The negative predictive value of the test is limited by false negatives in sarcomatoid mesothelioma.[79] Positive results have also been recognised in bronchogenic adenocarcinoma, metastatic pancreatic carcinoma, lymphoma and ovarian carcinoma.[76 78 81]

A positive serum or pleural fluid mesothelin level is highly suggestive of pleural malignancy and might be used to expedite a tissue diagnosis, but a negative result cannot be considered reassuring. Pleural fluid mesothelin has been shown to have additional value beyond pleural fluid cytology in the diagnosis of mesothelioma and might be used for its positive predictive value to clarify indeterminate cytology results.[80] Although mesothelin has a greater diagnostic accuracy than other tumour markers, its real clinical utility in the investigation of an undiagnosed pleural effusion, particularly in combination with routine clinical and radiological assessment, warrants further study before its use can be routinely recommended.

FURTHER DIAGNOSTIC IMAGING

Computed tomography (CT)

- **CT scans for pleural effusion should be performed with contrast enhancement of the pleura and before complete drainage of pleural fluid. (C)**
- **CT scans should be performed in the investigation of all undiagnosed exudative pleural effusions and can be useful in distinguishing malignant from benign pleural thickening. (C)**
- **A CT scan should be requested for complicated pleural infection when initial tube drainage has been unsuccessful and surgery is to be considered. (C)**

When investigating a pleural effusion, a contrast-enhanced thoracic CT scan should be performed before full drainage of the fluid as pleural abnormalities will be better visualised.[82] Free-flowing pleural fluid is seen as a sickle-shaped opacity in the most dependent part of the thorax. Suspended air bubbles within the fluid imply septations (figure 4), but CT does not distinguish the internal characteristics of pleural fluid with the same sensitivity as ultrasound.[17]

CT is particularly helpful in the diagnosis of empyema when the pleura enhances intensely around the fluid which usually forms a lenticular opacity (figure 4).[83 84] CT also distinguishes empyemas from lung abcesses.

There are features of contrast-enhanced thoracic CT scanning which can help differentiate between benign and malignant disease (figure 5). In a study of 74 patients, 39 of whom had malignant disease, Leung *et al* showed that malignant disease is favoured by nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening >1 cm and circumferential pleural thickening. These features had specificities of 94%, 94%, 88% and 100%, respectively, and sensitivities of 51%, 36%, 56% and 41%.[85] The accuracy of the criteria of Leung *et al* for the detection of pleural malignancy has been confirmed in several prospective studies.[82 86] Differentiation of pleural mesothelioma

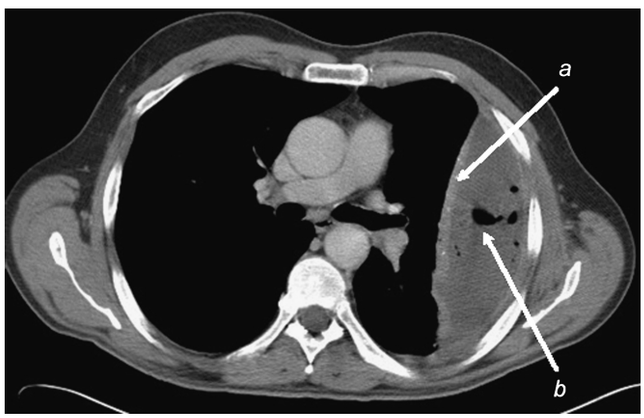

Figure 4 CT scan of left empyema with pleural enhancement (a) and suspended air bubbles (b).

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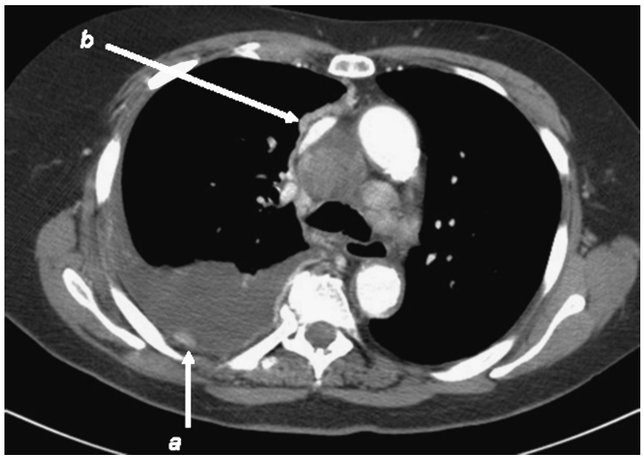

Figure 5 Right malignant pleural effusion with enhancing nodular pleural thickening (a) extending over the mediastinum (b).

from metastatic pleural malignancy is very difficult as the conditions share many CT features.

Magnetic resonance imaging (MRI)

MRI distinguishes accurately between benign and malignant pleural effusions via differences in signal intensity on T2-weighted images.[87] Distinction of morphological features of pleural malignancy by MRI has been shown in some studies to equal CT and assessment of diaphragmatic and chest wall involvement is superior.[88] Access to MRI is limited and it does not have a place in the routine investigation of pleural effusions at this time, but may be used to accurately assess pleural disease in patients for whom contrast is contraindicated. Dynamic contrast-enhanced MRI has shown promise in the monitoring of response of pleural mesothelioma to chemotherapy.[89]

PET-CT imaging

While the uptake of 18-fluorodeoxyglucose (FDG) has been shown to be greater in malignant pleural effusions, the value of PET-CT imaging in distinguishing benign and malignant disease is limited by false positives in patients with pleural inflammation including pleural infection and following talc pleurodesis.[90–92] PET-CT imaging does not currently have a role in the routine investigation of pleural effusions but, in common with dynamic contrast-enhanced MRI, there is emerging evidence suggesting a potential role in monitoring the response to treatment of pleural mesothelioma.[93–95]

INVASIVE INVESTIGATIONS

Percutaneous pleural biopsy

- **When investigating an undiagnosed effusion where malignancy is suspected and areas of pleural nodularity are shown on contrast-enhanced CT, an image-guided cutting needle is the percutaneous pleural biopsy method of choice. (A)**
- **Abrams needle biopsies are only diagnostically useful in areas with a high incidence of TB, although thoracoscopic and image-guided cutting needles have been shown to have a higher diagnostic yield. (C)**

A review of Abrams pleural biopsy yield from 2893 examinations showed a diagnostic rate of only 57% for malignancy.[96] The yield over pleural fluid cytology alone is increased by only 7–27% for malignancy.[68 69] Complications of Abrams pleural biopsy include site pain (1–15%), pneumothorax (3–15%), vasovagal reaction (1–5%), haemothorax (<2%), site haematoma (<1%), transient fever (<1%) and, very rarely, death secondary to haemorrhage.

The contrast-enhanced thoracic CT scan of a patient with a pleural effusion will often show a focal area of abnormal pleura. An image-guided cutting needle biopsy allows that focal area of abnormality to be biopsied. It has a higher yield than that of blind pleural biopsy in the diagnosis of malignancy. This technique is particularly useful in patients who are unsuitable for thoracoscopy.

Pleural malignant deposits tend to predominate close to the midline and diaphragm, which are areas best avoided when performing an Abrams biopsy. However, these anatomical regions are possible to biopsy safely under radiological imaging. In a recent prospective study, 33 patients with a pleural effusion and pleural thickening demonstrated on contrast-enhanced CT underwent percutaneous image-guided pleural biopsy. Correct histological diagnosis was made in 21 of 24 (sensitivity 88%, specificity 100%) including 13 of 14 patients with mesothelioma (sensitivity 93%).[97] In a larger retrospective review of image-guided pleural biopsy in one department by a single radiologist, 18 of the 21 mesothelioma cases were correctly identified (sensitivity 86%, specificity 100%).[98]

Image-guided cutting needle biopsies have been shown to be superior to Abrams needle biopsies in the diagnostic yield for malignant disease. In a randomised controlled trial of 50 consecutive patients with cytology-negative suspected malignant pleural effusions, Abrams biopsy correctly diagnosed malignancy in 8/17 (sensitivity 47%, specificity 100%, negative predictive value 44%, positive predictive value 100%) and CT-guided biopsy correctly diagnosed malignancy in 13/15 (sensitivity 87%, specificity 100%, negative predictive value 80%, positive predictive value 100%).[99]

In a prospective trial comparing local anaesthetic thoracoscopy with Abrams biopsy in an area with a high prevalence of TB,[100] thoracoscopy was found to have a combined culture/histology sensitivity of 100% compared with 79% for Abrams pleural biopsy. The technique with the highest diagnostic rate for tuberculous pleuritis on the basis of published evidence is therefore local anaesthetic thoracoscopy. However, since blind pleural biopsy has reasonably high sensitivity and is likely to be more cost effective as an initial diagnostic procedure, it will often be the procedure of first choice in resource-poor areas with a high incidence of TB. Blind pleural biopsy cannot be justified for the diagnosis of TB where the incidence is not high enough to maintain operator experience (see evidence table C available on the BTS website at www.brit-thoracic.org.uk).

Thoracoscopy

- **Thoracoscopy is the investigation of choice in exudative pleural effusions where a diagnostic pleural aspiration is inconclusive and malignancy is suspected. (C)**

In patients with a symptomatic exudative pleural effusion where a diagnostic pleural aspiration is negative or inconclusive, thoracoscopy is suggested as the next choice investigation since the procedure will be relatively uncomplicated and pleurodesis is likely to be indicated.

Local anaesthetic thoracoscopy

Local anaesthetic thoracoscopy can be performed by physicians or surgeons and is a safe and well tolerated procedure. Major complications (eg, empyema, haemorrhage and pneumonia) occur in only 2.3% (95% CI 1.9% to 2.8%) and death is rare at

0.40% (95% CI 0.2% to 0.7%). It has a diagnostic sensitivity for malignant pleural disease of 92.6% (95% CI 91.0% to 93.9%).[101–121] It also has a higher diagnostic yield than blind pleural biopsy for tuberculous pleuritis. Talc poudrage can be administered at the end of the procedure which achieves a successful pleurodesis in 80–90% (see BTS guideline on thoracoscopy for further detail.

Video-assisted thoracoscopic surgery (VATS)

This is performed by thoracic surgeons and requires a general anaesthetic. It is therefore not a suitable option for frail individuals and those with other severe comorbidities. This procedure reports similarly high diagnostic sensitivity rates of approximately 95% for malignancy and is also relatively safe with a low complication rate. In one series of 566 examinations, the most common side effect was subcutaneous emphysema with cardiac dysrhythmia and air embolism occurring in <1% and no deaths.[122]

One advantage of VATS over local anaesthetic thoracoscopy is that the surgical operator is able to proceed to other thoracic surgical options, if appropriate, at the time of the procedure. In particular, a judgement can be made as to whether the lung is trapped or free to expand. In trapped lung syndrome, pleurodesis is likely to be less effective so an indwelling pleural catheter can be placed at the time of VATS (see BTS guideline on thoracoscopy.

Bronchoscopy

- **Routine diagnostic bronchoscopy should not be performed for undiagnosed pleural effusion. (C)**
- **Bronchoscopy should be considered if there is haemoptysis or clinical or radiographic features suggestive of bronchial obstruction. (C)**

Bronchoscopy has a limited role in the investigation of patients with an undiagnosed pleural effusion as its diagnostic yield is very low.[123–126] It should be reserved for patients whose radiology suggests the presence of a mass or loss of volume or when there is a history of haemoptysis, possible aspiration of a foreign body or a trapped lung with a suspicion of a proximal lung mass.

If bronchoscopy is deemed necessary, it should be performed after pleural drainage in order to perform adequate examination without extrinsic airway compression by pleural fluid.

SPECIFIC CONDITIONS AND TESTS

Tuberculous pleurisy

- **When pleural biopsies are taken, they should be sent for both histological examination and culture to improve the diagnostic sensitivity for TB. (B)**
- **Thoracoscopic pleural biopsies are the test most likely to yield positive mycobacterial culture (and therefore drug sensitivity) results. (B)**
- **Surrogate markers of pleural TB are useful 'rule out' tests in low incidence countries. Adenosine deaminase is the most thoroughly validated to date. (B)**

Tuberculous pleuritis is a type IV hypersensitivity reaction to mycobacterial protein and the mycobacterial load in the pleural fluid is usually low. Pleural fluid microscopy for acid-fast bacilli therefore has a sensitivity of <5% and pleural fluid culture of 10–20%.[127] Thoracoscopic pleural biopsy has been shown to have a sensitivity of >70% for culture of pleural tissue and overall diagnostic sensitivity approaches 100% when evidence of caseating granulomas on pleural biopsy histology is combined with culture.[100]

Surrogate markers of pleural TB

Tuberculous pleuritis is a treatable cause of a lymphocytic pleural effusion. It is desirable to exclude the diagnosis in patients with lymphocytic effusions, avoiding inappropriate and side effect-prone empirical antituberculous therapy. In patients who are unfit for invasive investigations, pleural fluid or blood biomarkers of infection can be useful. Adenosine deaminase (ADA) is an enzyme present in lymphocytes, and its level in pleural fluid is significantly raised in most tuberculous pleural effusions. A meta-analysis of 63 studies on the diagnostic use of ADA confirmed a sensitivity of 92%, specificity 90% and positive and negative likelihood ratios of 9.0 and 0.10, respectively.[128] Raised ADA levels can also be seen in empyema, rheumatoid pleurisy and, occasionally, in malignancy. Restricting the use of ADA to lymphocytic effusions or measurement of isoenzyme ADA-2 can reduce the false positives significantly.[129] ADA is very cheap and quick to perform and remains stable when stored at 4°C for up to 28 days.[130] It is useful in patients with HIV or those immunosuppressed (eg, renal transplant). In countries with a low prevalence of TB, ADA is a useful 'rule out' test.

Unstimulated interferon γ levels in pleural fluid have also been shown to have similar diagnostic accuracy as ADA in a meta-analysis.[131] The former, however, is more expensive. Interferon γ release assays (IGRAs) have been studied. Applied to blood in areas with a low incidence of TB, sensitivities as high as 90% have been reported but specificity is limited by an inability of the tests to distinguish latent from active TB.[132] Small studies have applied IGRAs to pleural fluid with demonstration of superior sensitivities (96.4%), although the commercial tests are not yet validated for fluids other than blood.[133] While further studies are awaited, overall diagnostic performance, ease of use and cost are unlikely to rival that of ADA.[134]

In well-resourced healthcare settings, the greatest chance of obtaining mycobacterial culture and sensitivities should be pursued via thoracoscopic pleural biopsies. However, a large review of 7549 cases of tuberculous pleuritis by the Center for Disease Control showed that drug resistance patterns of pleural TB in the USA broadly reflected those of pulmonary TB in the same region.[135] If mycobacterial culture and sensitivities are not achieved, the treatment regime should reflect that of the local resistance patterns.

Connective tissue diseases

Rheumatoid arthritis and systemic lupus erythematosus (SLE) are the most common connective tissue diseases to involve the pleura. Pleural effusions occur in connective tissue disease due to primary autoimmune pleuritis or secondary to renal, cardiac, thromboembolic disease or drug therapy.

Rheumatoid arthritis-associated pleural effusions

- **Most chronic pleural effusions secondary to rheumatoid arthritis have a very low glucose level of <1.6 mmol/l (29 mg/dl). (D)**

Pleural involvement occurs in 5% of patients with rheumatoid arthritis.[136] Rheumatoid arthritis-associated pleural effusions occur more frequently in men, although the disease itself is more common in women.[137] Chronic rheumatoid effusions are the most common cause of pseudochylous (cholesterol) effusions in countries with a low incidence of TB, but they can also be serous or haemorrhagic in appearance.[138 139] The measurement of triglycerides and cholesterol in milky effusions will confirm the diagnosis of a pseudochylous picture and, in the presence of

rheumatoid arthritis, this makes other causes for the effusion unlikely. Rheumatoid arthritis is unlikely to be the cause of a chronic effusion if the glucose level in the fluid is >1.6 mmol/l, serving as a useful screening test.[58] 80% of rheumatoid pleural effusions have a pleural fluid glucose to serum ratio of <0.5 and a pH <7.30.[140] However, in acute rheumatoid pleurisy, the glucose and pH may be normal.[141] Measurement of C4 complement in pleural fluid may be of additional help, with levels <0.04 g/l in all cases of rheumatoid pleural disease and in only 2 of 118 controls reported in one study.[141] Rheumatoid factor can be measured on the pleural fluid and often has a titre of >1:320.[142] However, it can be present in effusions of other aetiology and often mirrors the serum value, adding little diagnostically.[141]

Systemic lupus erythematosus (SLE)

- **Pleural fluid antinuclear antibodies should not be measured routinely as it reflects the serum level and is therefore usually unhelpful. (C)**

Pleuritis is the first manifestation of SLE in 5–10% of patients but is an early feature in 25–30% and is usually accompanied by multisystem involvement. Pleural effusions are frequently small and are bilateral in 50% of patients.[143]

No test definitively positively distinguishes SLE pleuritis from other causes of exudative effusions. Biochemical features are not distinctive or consistent.[144 145] Elevated pleural fluid antinuclear antibodies (ANA) and an increased pleural fluid to serum ANA ratio is suggestive of SLE pleuritis, but elevation is also sometimes seen in malignant effusions.[146] Porcel *et al* measured pleural fluid ANA titres in 266 patients with pleural effusions of established cause including 15 with SLE pleuritis. They demonstrated a sensitivity of 100% (95% CI 97% to 100%) and a specificity of 94% (95% CI 91% to 97%) for the pleural fluid test but, consistent with previous reports, the results were identical when testing serum.[147] There is no additional value in measuring pleural fluid ANA above the serum test.

Pleural effusions due to pulmonary embolism

Pleural effusions detectable on chest x-ray occur in 23–48% of patients with pulmonary emboli.[148] Effusions are small (less than one-third of the hemithorax) in up to 90% of cases, although moderate and massive effusions are also recognised.[3] They may be ipsilateral, contralateral or bilateral relative to the radiologically-detected embolus.[2 3]

Recent series applying Light's criteria have found that pleural effusions associated with pulmonary embolism are always exudates.[3 149] Fluid characteristics, however, are non-specific and unhelpful in making the diagnosis which should be pursued radiologically, given a high index of clinical suspicion or in the context of an effusion that remains undiagnosed after standard baseline investigations.

Chylothorax and pseudochylothorax

- **If a chylothorax or pseudochylothorax is suspected, pleural fluid should be tested for cholesterol crystals and chylomicrons and the pleural fluid triglyceride and cholesterol levels measured. (C)**

If the pleural fluid appears milky, chylothorax and pseudochylothorax must be considered. Occasionally an empyema can be sufficiently turbid to be confused with chyle. They can be distinguished by bench centrifugation which leaves a clear supernatant in empyema while chylous effusion remains milky. It should be noted that, in starved patients, chyle may not appear milky.

Box 6 Common causes of chylothorax and pseudochylothorax

Chylothorax

- Trauma: thoracic surgery (especially if involving posterior mediastinum, eg oesophagectomy), thoracic injuries
- Neoplasm: lymphoma or metastatic carcinoma
- Miscellaneous: disorders of lymphatics (including lymphangioleiomyomatosis), tuberculosis, cirrhosis, obstruction of central veins, chyloascites
- Idiopathic (about 10%)

Pseudochylothorax

- Tuberculosis
- Rheumatoid arthritis

True chylous effusions (chylothorax) result from disruption of the thoracic duct or its tributaries such that chyle is present in the pleural space.

Trauma, particularly following thoracic surgery, probably causes about 50% with medical causes including malignancy (particularly lymphoma), TB and lymphatic malformations accounting for most of the remaining half (box 6).[150]

Unlike other exudative effusions, the diagnosis of chylothorax or its underlying cause cannot usually be established from thoracoscopy or pleural biopsies. In non-surgical cases, a CT scan of the thorax to exclude mediastinal pathology (especially lymphoma) is mandatory. The site of leak may be demonstrated by lymphangiography.

Chylothorax must be distinguished from pseudochylothorax or 'cholesterol pleurisy' which results from the accumulation of cholesterol crystals. Rheumatoid pleurisy and tuberculous pleuritis are the most commonly reported causes of a pseudochylous effusion.[138 151] Pseudochylothorax usually arises from chronic (often years) pleural effusion and the pleura is usually markedly thickened.[152] Exceptions do exist and clinicians are encouraged not to discard the diagnosis in the absence of chronicity and thickened pleura.[153]

Chylothorax and pseudochylothorax can be discriminated by lipid analysis of the fluid. Demonstration of chylomicrons confirms a chylothorax, whereas the presence of cholesterol crystals diagnoses pseudochylothorax. A true chylothorax will usually have a high triglyceride level, usually >1.24 mmol/l (110 mg/dl) and can usually be excluded if the triglyceride level is <0.56 mmol/l (50 mg/dl). In a pseudochylothorax a cholesterol level >5.18 mmol/l (200 mg/dl) or the presence of cholesterol crystals is diagnostic irrespective of triglyceride levels (see table 4).[152–154]

Chylothorax can be a result of transdiaphragmatic migration of chylous ascites, which can be secondary to hepatic cirrhosis. In these cases, the pleural effusion is often a transudate.

Table 4 Pleural fluid lipid values in pseudochylothorax and cylothorax

Feature	Pseudochylothorax	Chylothorax
Triglycerides		>1.24 mmol/l (110 mg/dl)
Cholesterol	>5.18 mmol/l (200 mg/dl)	Usually low
Cholesterol crystals	Often present	Absent
Chylomicrons	Absent	Usually present

Table 5 Other important causes of pleural effusions

Condition	Clinical features	Pleural fluid characteristics	Special investigations and management
Early post-CABG pleural effusion[158]	Occur within 30 days of CABG. Left > right. Most small and asymptomatic. Prevalence 89% at 7 days postoperatively	Exudate. Bloody (haematocrit >5%). Often eosinophilic	Only perform diagnostic aspiration if the patient is febrile, complains of pleuritic chest pain or the effusion is very large. Most settle spontaneously
Late post-CABG pleural effusion[159]	Occur >30 days post-CABG. Left > right. May be large and associated with dyspnoea	Exudate. Clear/yellow. Lymphocytic	Diagnostic aspiration to exclude other causes and confirm the diagnosis. Repeated therapeutic thoracentesis usually successful for symptomatic effusions.
Urinothorax[160]	Due to obstructive uropathy. Urine tracks through the retroperitoneum to the pleural space.	Pleural fluid creatinine > serum creatinine. Transudate. Low pH	Usually resolves with relief of the renal obstruction
Ovarian hyperstimulation syndrome[161]	Life-threatening reaction to ovulation induction (hCG or clomiphene). May be pleural effusion alone (usually right sided) or whole syndrome with: massive ascites, renal and hepatic failure, thromboemboli and ARDS	Exudate with both protein and LDH in exudative range	Repeated therapeutic aspirations often required to relieve dyspnoea
Lymphoma-related pleural effusion[162]	Effusion may be associated with mediastinal lymphadenopathy on CT but often there are no clinical features to distinguish from other causes of pleural effusion	Exudate. Lymphocytic. Positive cytology in around 40%. Chylothorax in around 15%	Pleural fluid flow cytometry and cytogenetics may be useful. Thoracoscopic pleural biopsies are often negative but required to exclude other causes if diagnosis unclear

ARDS, adult respiratory distress syndrome; CABG, coronary artery bypass graft; hCG, human chorionic gonadotrophin.

Benign asbestos pleural effusion

Benign asbestos pleural effusions are commonly diagnosed in the first two decades after asbestos exposure. The prevalence is dose-related with a shorter latency period than other asbestos-related disorders.[155] The effusion is usually small and asymptomatic, often with pleural fluid which is haemorrhagic.[156 157] There is a propensity for the effusion to resolve within 6 months, leaving behind residual diffuse pleural thickening.[156 157] As there are no definitive tests, the diagnosis can only be made with certainty after a prolonged period of follow-up and consideration should be given to early thoracoscopy with pleural biopsy in any patient with a pleural effusion and a history of asbestos exposure, particularly in the presence of chest pain. Table 5 summarises clinical and pleural fluid characteristics of other important causes of unilateral pleural effusions.

MANAGEMENT OF PERSISTENT UNDIAGNOSED EFFUSIONS

Even after a complete investigation including thoracoscopic biopsies, a significant number of patients with pleural exudates are diagnosed with 'non-specific pleuritis' and no specific diagnosis can be made. A retrospective study of 75 such patients found that only 8.3% of these turned out to be malignant over a 2-year follow-up period. The majority of patients with non-specific pleuritis (91.7%) followed a benign course, with spontaneous resolution of the effusion in 81.8% of cases.[163]

In patients not fit enough for thoracoscopy, it is sensible to reconsider diagnoses with a specific treatment (eg, TB, pulmonary embolism, lymphoma and chronic heart failure). A considerable number of undiagnosed pleural effusions in this category are due to a malignant process. Watchful waiting may be the appropriate management in this setting.

Competing interests No member of the Guideline Group is aware of any competing interests.

Provenance and peer review The draft guideline was available for online public consultation (July/August 2009) and presented to the BTS Winter Meeting (December 2009). Feedback was invited from a range of stakeholder institutions (see Introduction). The draft guideline was reviewed by the BTS Standards of Care Committee (September 2009).

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Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010

Andrew MacDuff,[1] Anthony Arnold,[2] John Harvey,[3] on behalf of the BTS Pleural Disease Guideline Group

[1]Respiratory Medicine, Royal Infirmary of Edinburgh, UK
[2]Department of Respiratory Medicine, Castle Hill Hospital, Cottingham, East Yorkshire, UK
[3]North Bristol Lung Centre, Southmead Hospital, Bristol, UK

Correspondence to
Dr John Harvey, North Bristol Lung Centre, Southmead Hospital, Bristol BS10 5NB, UK; john.harvey@nbt.nhs.uk

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INTRODUCTION

The term 'pneumothorax' was first coined by Itard and then Laennec in 1803 and 1819 respectively,[1] and refers to air in the pleural cavity (ie, interspersed between the lung and the chest wall). At that time, most cases of pneumothorax were secondary to tuberculosis, although some were recognised as occurring in otherwise healthy patients ('pneumothorax simple'). This classification has endured subsequently, with the first modern description of pneumothorax occurring in healthy people (primary spontaneous pneumothorax, PSP) being that of Kjærgaard[2] in 1932. It is a significant global health problem, with a reported incidence of 18–28/100 000 cases per annum for men and 1.2–6/100 000 for women.[3]

Secondary pneumothorax (SSP) is associated with underlying lung disease, in distinction to PSP, although tuberculosis is no longer the commonest underlying lung disease in the developed world. The consequences of a pneumothorax in patients with pre-existing lung disease are significantly greater, and the management is potentially more difficult. Combined hospital admission rates for PSP and SSP in the UK have been reported as 16.7/100 000 for men and 5.8/100 000 for women, with corresponding mortality rates of 1.26/million and 0.62/million per annum between 1991 and 1995.[4]

With regard to the aetiology of pneumothorax, anatomical abnormalities have been demonstrated, even in the absence of overt underlying lung disease. Subpleural blebs and bullae are found at the lung apices at thoracoscopy and on CT scanning in up to 90% of cases of PSP,[5 6] and are thought to play a role. More recent autofluorescence studies[7] have revealed pleural porosities in adjacent areas that were invisible with white light. Small airways obstruction, mediated by an influx of inflammatory cells, often characterises pneumothorax and may become manifest in the smaller airways at an earlier stage with 'emphysema-like changes' (ELCs).[8]

Smoking has been implicated in this aetiological pathway, the smoking habit being associated with a 12% risk of developing pneumothorax in healthy smoking men compared with 0.1% in non-smokers.[9] Patients with PSP tend to be taller than control patients.[10 11] The gradient of negative pleural pressure increases from the lung base to the apex, so that alveoli at the lung apex in tall individuals are subject to significantly greater distending pressure than those at the base of the lung, and the vectors in theory predispose to the development of apical subpleural blebs.[12]

Although it is to some extent counterintuitive, there is no evidence that a relationship exists between the onset of pneumothorax and physical activity, the onset being as likely to occur during sedentary activity.[13]

Despite the apparent relationship between smoking and pneumothorax, 80–86% of young patients continue to smoke after their first episode of PSP.[14] The risk of recurrence of PSP is as high as 54% within the first 4 years, with isolated risk factors including smoking, height and age >60 years.[12 15] Risk factors for recurrence of SSP include age, pulmonary fibrosis and emphysema.[15 16] Thus, efforts should be directed at smoking cessation after the development of a pneumothorax.

The initial British Thoracic Society (BTS) guidelines for the treatment of pneumothoraces were published in 1993.[17] Later studies suggested that compliance with these guidelines was improving but remained suboptimal at only 20–40% among non-respiratory and A&E staff. Clinical guidelines have been shown to improve clinical practice,[18 19] compliance being related to the complexity of practical procedures[20] and strengthened by the presence of an evidence base.[21] The second version of the BTS guidelines was published in 2003[22] and reinforced the trend towards safer and less invasive management strategies, together with detailed advice on a range of associated issues and conditions. It included algorithms for the management of PSP and SSP but excluded the management of trauma. This guideline seeks to consolidate and update the pneumothorax guidelines in the light of subsequent research and using the SIGN methodology. Traumatic pneumothorax is not covered by this guideline.

- **SSP is associated with a higher morbidity and mortality than PSP. (D)**
- **Strong emphasis should be placed on smoking cessation to minimise the risk of recurrence. (D)**
- **Pneumothorax is not usually associated with physical exertion. (D)**

CLINICAL EVALUATION

- **Symptoms in PSP may be minimal or absent. In contrast, symptoms are greater in SSP, even if the pneumothorax is relatively small in size. (D)**
- **The presence of breathlessness influences the management strategy. (D)**
- **Severe symptoms and signs of respiratory distress suggest the presence of tension pneumothorax. (D)**

The typical symptoms of chest pain and dyspnoea may be relatively minor or even absent,[23] so that

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a high index of initial diagnostic suspicion is required. Many patients (especially those with PSP) therefore present several days after the onset of symptoms.[24] The longer this period of time, the greater is the risk of re-expansion pulmonary oedema (RPO).[25 26] In general, the clinical symptoms associated with SSP are more severe than those associated with PSP, and most patients with SSP experience breathlessness that is out of proportion to the size of the pneumothorax.[27 28] These clinical manifestations are therefore unreliable indicators of the size of the pneumothorax.[29 30] When severe symptoms are accompanied by signs of cardiorespiratory distress, tension pneumothorax must be considered.

The physical signs of a pneumothorax can be subtle but, characteristically, include reduced lung expansion, hyper-resonance and diminished breath sounds on the side of the pneumothorax. Added sounds such as 'clicking' can occasionally be audible at the cardiac apex.[23] The presence of observable breathlessness has influenced subsequent management in previous guidelines.[17 23] In association with these signs, cyanosis, sweating, severe tachypnoea, tachycardia and hypotension may indicate the presence of tension pneumothorax (see later section).

Arterial blood gas measurements are frequently abnormal in patients with pneumothorax, with the arterial oxygen tension (Pa_{O_2}) being <10.9 kPa in 75% of patients,[31] but are not required if the oxygen saturations are adequate (>92%) on breathing room air. The hypoxaemia is greater in cases of SSP,[31] the Pa_{O_2} being <7.5 kPa, together with a degree of carbon dioxide retention in 16% of cases in a large series.[32] Pulmonary function tests are poor predictors of the presence or size of a pneumothorax[7] and, in any case, tests of forced expiration are generally best avoided in this situation.

The diagnosis of pneumothorax is usually confirmed by imaging techniques (see below) which may also yield information about the size of the pneumothorax, but clinical evaluation should probably be the main determinant of the management strategy as well as assisting the initial diagnosis.

IMAGING

Initial diagnosis

- **Standard erect chest x-rays in inspiration are recommended for the initial diagnosis of pneumothorax, rather than expiratory films. (A)**
- **The widespread adoption of digital imaging (PACS) requires diagnostic caution and further studies since the presence of a small pneumothorax may not be immediately apparent. (D)**
- **CT scanning is recommended for uncertain or complex cases. (D)**

The following numerous imaging modalities have been employed for the diagnosis and management of pneumothorax:

1. Standard erect PA chest x-ray.
2. Lateral x-rays.
3. Expiratory films.
4. Supine and lateral decubitus x-rays.
5. Ultrasound scanning.
6. Digital imaging.
7. CT scanning.

Standard erect PA chest x-ray

This has been the mainstay of clinical management of primary and secondary pneumothorax for many years, although it is acknowledged to have limitations such as the difficulty in accurately quantifying pneumothorax size. Major technological advances in the last decade have resulted in the advent of digital chest imaging, so that conventional chest films are no longer easily available in clinical practice in the UK or in many other modern healthcare systems. The diagnostic characteristic is displacement of the pleural line. In up to 50% of cases an air-fluid level is visible in the costophrenic angle, and this is occasionally the only apparent abnormality.[33] The presence of bullous lung disease can lead to the erroneous diagnosis of pneumothorax, with unfortunate consequences for the patient. If uncertainty exists, then CT scanning is highly desirable (see below).

Lateral x-rays

These may provide additional information when a suspected pneumothorax is not confirmed by a PA chest film[33] but, again, are no longer routinely used in everyday clinical practice.

Expiratory films

These are not thought to confer additional benefit in the routine assessment of pneumothorax.[34–36]

Supine and lateral decubitus x-rays

These imaging techniques have mostly been employed for trauma patients who cannot be safely moved. They are generally less sensitive than erect PA x-rays for the diagnosis of pneumothorax[37 38] and have been superseded by ultrasound or CT imaging for patients who cannot assume the erect posture.

Ultrasound scanning

Specific features on ultrasound scanning are diagnostic of pneumothorax[39] but, to date, the main value of this technique has been in the management of supine trauma patients.[40]

Digital imaging

Digital radiography (Picture-Archiving Communication Systems, PACS) has replaced conventional film-based chest radiography across most UK hospitals within the last 5 years, conferring considerable advantages such as magnification, measurement and contrast manipulation, ease of transmission, storage and reproduction. Relatively few studies have addressed the specific issue of pneumothorax and its diagnosis, and these have tended to focus on expert diagnosis (by consultant radiologists) and the more discriminating departmental (rather than ward-based) workstations. Even so, some difficulties were found in the diagnosis of pneumothorax in early studies.[41 42] Since then there have been technological advances, such that digital imaging may now be as reliable as more conventional chest x-rays in pneumothorax diagnosis, but there have been no more recent studies to confirm this. Differences exist between the characteristics (screen size, pixel count, contrast and luminescence) and therefore the sensitivity of the more expensive departmental devices and the desktop and mobile consoles available in the ward environment. It is currently recommended that, where primary diagnostic decisions are made based on the chest x-ray, a diagnostic PACS workstation is available for image review.

In addition, digital images do not directly lend themselves to measurement and size calculations; an auxiliary function and use of a cursor is required, but this is almost certainly more accurate than using a ruler and is easy to learn to do. Non-specialist clinicians and trainees may not always be familiar with these functions.

CT scanning

This can be regarded as the 'gold standard' in the detection of small pneumothoraces and in size estimation.[43] It is also useful

in the presence of surgical emphysema and bullous lung disease[44] and for identifying aberrant chest drain placement[45] or additional lung pathology. However, practical constraints preclude its general use as the initial diagnostic modality.

Size of pneumothorax

- **In defining a management strategy, the size of a pneumothorax is less important than the degree of clinical compromise. (D)**
- **The differentiation of a 'large' from a 'small' pneumothorax continues to be the presence of a visible rim of >2 cm between the lung margin and the chest wall (at the level of the hilum) and is easily measured with the PACS system. (D)**
- **Accurate pneumothorax size calculations are best achieved by CT scanning. (C)**

The size of pneumothoraces does not correlate well with the clinical manifestations.[29 30] The clinical symptoms associated with secondary pneumothoraces are more severe in general than those associated with primary pneumothoraces, and may seem out of proportion to the size of the pneumothorax.[27 28] The clinical evaluation is therefore probably more important than the size of the pneumothorax in determining the management strategy.

Commonly, the plain PA chest x-ray has been used to quantify the size of the pneumothorax. However, it tends to underestimate the size because it is a two-dimensional image while the pleural cavity is a three-dimensional structure. The 2003 BTS guidelines[22] advocated a more accurate means of size calculation than its predecessor in 1993,[15] using the cube function of two simple measurements, and the fact that a 2 cm radiographic pneumothorax approximates to a 50% pneumothorax by volume. There are difficulties with this approach, including the fact that some pneumothoraces are localised (rather than uniform), so that measurement ratios cannot be applied. The shape of the lung cannot be assumed to remain constant during collapse.[46] The measurement of the ratio of the lung to the hemithorax diameter is accurate and relatively easy with the new PACS systems by means of a cursor, once familiar with the PACS auxiliary functions.

The choice of a 2 cm depth is a compromise between the theoretical risk of needle trauma with a more shallow pneumothorax and the significant volume and length of time to spontaneous resolution of a greater depth of pneumothorax.[47 48] Assuming a symmetrical pattern of lung collapse, then this measure is normally taken from the chest wall to the outer edge of the lung at the level of the hilum (figure 1). Guidelines from the USA[49] estimated the volume of a pneumothorax by measuring the distance from the lung apex to the cupola, but this method would tend to overestimate the volume in a localised apical pneumothorax. Belgian guidelines have used yet another technique for measuring pneumothorax size, and comparisons between the different techniques have shown poor agreement.[50]

CT scanning is regarded as the best means of establishing the size of a pneumothorax[51] and has been calibrated in a lung model experiment.[52]

TREATMENT OPTIONS FOR PNEUMOTHORAX

- **Patients with pre-existing lung disease tolerate a pneumothorax less well, and the distinction between PSP and SSP should be made at the time of diagnosis to guide appropriate management. (D)**

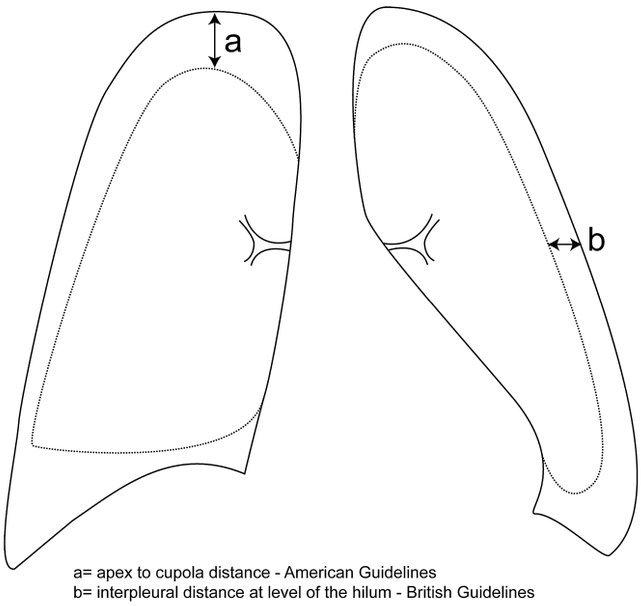

Figure 1 Depth of pneumothorax.

- **Breathlessness indicates the need for active intervention as well as supportive treatment (including oxygen). (D)**
- **The size of the pneumothorax determines the rate of resolution and is a relative indication for active intervention. (D)**

Primary pneumothorax occurs in patients with no evidence of other underlying lung disease. Although histological abnormalities are usually present, associated in particular with cigarette smoking, they have not been manifested by symptoms or loss of function. In contrast, secondary pneumothorax usually occurs in patients with overt underlying lung disease, most commonly chronic obstructive pulmonary disease (COPD). It is important to make this fundamental distinction as pneumothorax in COPD is much less well tolerated by the patient and tends to respond less favourably to management interventions and because the underlying lung disease requires appropriate treatment in addition. Several series have shown a reduced success rate for aspiration in patients aged >50 years as well as for chronic lung disease. It seems likely that these older patients had unrecognised underlying lung disease. This age criterion was included in the flowchart for SSP in the 2003 guidelines and is incorporated into the new flowchart (figure 2), serving as a prompt to consider the likelihood of SSP. Further criteria that are important in the decision-making process are the presence of significant breathlessness and the size of the pneumothorax. The rate of resolution/reabsorption of spontaneous pneumothoraces has been gauged as being between 1.25% and 2.2% of the volume of the hemithorax every 24 h,[47 48 52] the higher and more recent estimate[52] being derived from CT volumetry. Thus, a complete pneumothorax might be expected to take up to 6 weeks to resolve spontaneously and, conceivably, in the presence of a persistent air leak, even longer.

Management of PSP

- **Patients with PSP or SSP and significant breathlessness associated with any size of pneumothorax should undergo active intervention. (A)**
- **Chest drains are usually required for patients with tension or bilateral pneumothorax who should be admitted to hospital. (D)**

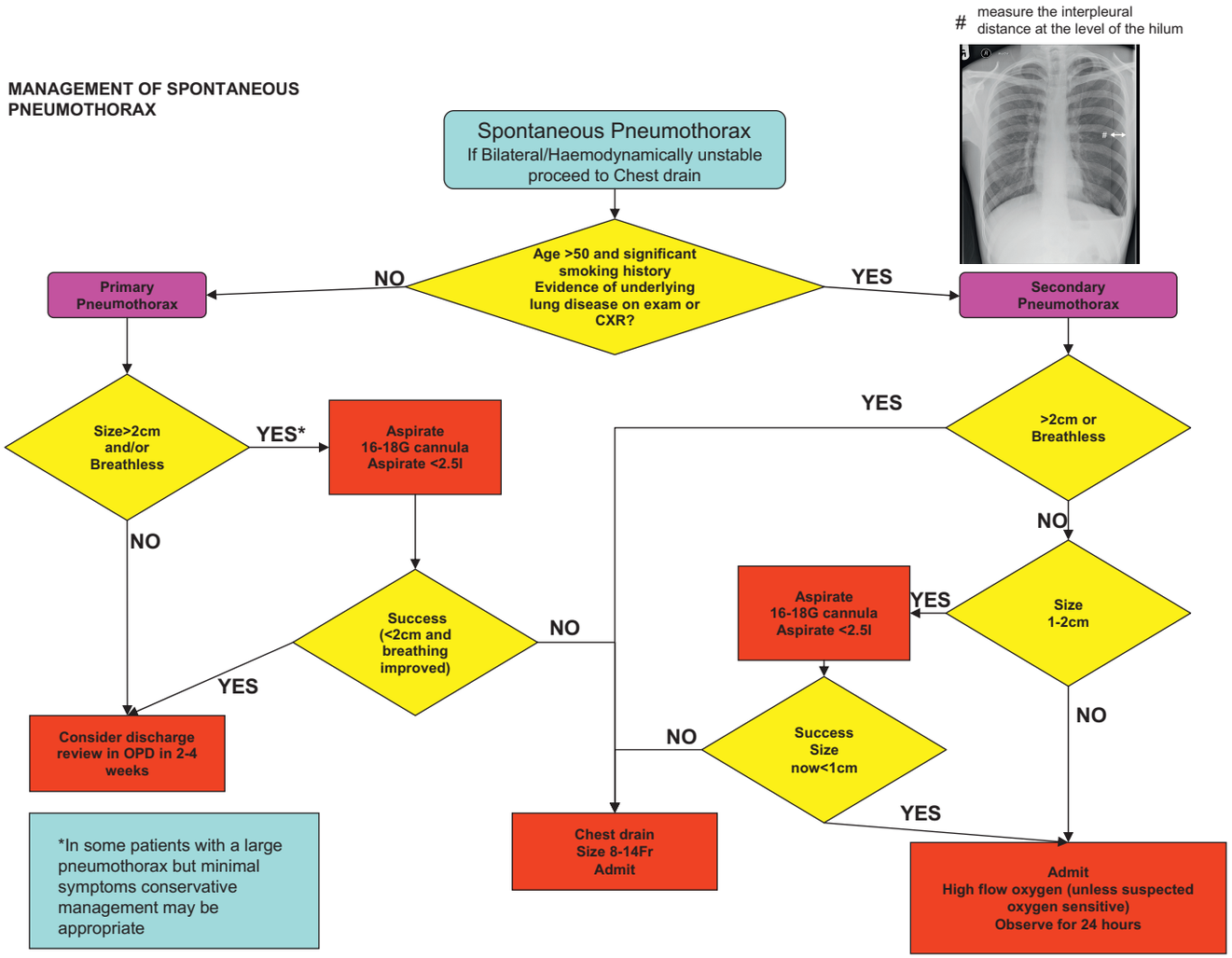

Figure 2 Flowchart of management of spontaneous pneumothorax.

- **Observation is the treatment of choice for small PSP without significant breathlessness. (B)**
- **Selected asymptomatic patients with a large PSP may be managed by observation alone. (A)**
- **Patients with a small PSP without breathlessness should be considered for discharge with early outpatient review. These patients should also receive clear written advice to return in the event of worsening breathlessness. (D)**

Both tension pneumothorax and bilateral pneumothorax are potentially life-threatening events that require chest drain insertion. Because such patients are generally excluded from trials of spontaneous pneumothorax, there is no evidence upon which to base recommendations, advice being based on the grounds of safe practice. Similarly, patients with associated large pleural effusions (hydropneumothorax) have also been excluded from trials, but are likely to require chest drain insertion and further investigation (see separate guideline). A summary of the management recommendations is shown in the flowchart (figure 2) with explanatory detail in the text below.

Minimal symptoms

Conservative management of small pneumothoraces has been shown to be safe,[47 53 54] and patients who are not breathless can be managed as outpatients providing they can easily seek medical attention if any deterioration in their symptoms occurs. Up to 80% of pneumothoraces estimated as smaller than 15% have no persistent air leak, and recurrence in those managed with observation alone is less than in those treated by chest drains.[55] Early review is advisable to ensure satisfactory resolution and to reinforce the advice on lifestyle. There is no evidence that active intervention improves the associated pain, which simply warrants appropriate analgesia.

Symptomatic pneumothorax

Observation alone is inappropriate for breathless patients who require active intervention (needle aspiration or chest drain insertion). Marked breathlessness in a patient with a small PSP may herald tension pneumothorax.[55] If a patient is hospitalised for observation, supplemental high flow oxygen should be given where feasible. As well as correcting any arterial hypoxaemia,[56] it has been shown to result in a fourfold increase in the rate of pneumothorax resolution.[57] In the presence of a continued air leak, the mechanism may be a reduction in the partial pressure of nitrogen in the pleural space relative to oxygen, which is more readily absorbed. Also, a similar effect in the pleural capillaries creates a more favourable resorption gradient.[58]

Needle aspiration or chest drain?

- **Needle (14–16 G) aspiration (NA) is as effective as large-bore (>20 F) chest drains and may be associated with reduced hospitalisation and length of stay. (A)**

- **NA should not be repeated unless there were technical difficulties. (B)**
- **Following failed NA, small-bore (<14 F) chest drain insertion is recommended. (A)**
- **Large-bore chest drains are not needed for pneumothorax. (D)**

Needle aspiration (NA) was recommended in the previous guidelines[17 22] as the initial intervention for PSP on the basis of studies[59 60] showing equivalent success to the insertion of large-bore chest drains, although this was not shown in another study.[61] Seldinger (catheter over guide wire) chest drains have entered widespread usage since then and further studies have been published. A randomised controlled trial in a Kuwaiti population has confirmed equivalence between NA and chest drains (16 Fr), plus a reduction in hospital admission and length of stay for NA.[62] A smaller study in India has also confirmed equivalence.[63] Two recent case series have reported NA success rates of 69%[64] and 50.5%.[65] Several meta-analyses[66–68] were limited by the small numbers of patients and studies[69–77] but confirm equivalence, with NA success rates ranging from 30% to 80% (see evidence table available on the BTS website www.brit-thoracic.org.uk). If undertaken, NA should cease after 2.5 l of air has been aspirated, further re-expansion being unlikely[59] because of the likely presence of a persistent air leak.

Guidelines that encourage NA are not always followed[78–82] and the ease of insertion of small-bore (<14 F) Seldinger chest drains may be regarded as a simpler option to NA. Their success has been documented in several studies,[83–89] the attachment of Heimlich valves facilitating mobilisation and outpatient care. Small-bore chest drains have been shown to have a similar success rate to larger drains[90] while being less painful,[91 92] but there have been no randomised controlled trials comparing them with NA. More detail on chest drain insertion and management and complications of chest drain insertion are found in the guideline on pleural procedures. Catheter aspiration was described in the last guideline,[22] with success in up to 59%, and further improvement with the addition of Heimlich valves and suction.[93–95] Seldinger chest drains have also permitted a 'stepwise' approach to PSP management, following a predefined pathway that culminates in surgical referral where there is a persistent air leak.[96]

The choice of initial intervention for PSP should take into account operator experience and patient choice; NA is less painful than chest drain insertion[60] but failure in approximately one-third of patients will require a second procedure. Other national and consensus guidelines recommend either NA or small-bore chest drain insertion,[97] or chest drain insertion alone.[49] We believe that NA remains the procedure of first choice in most cases. Repeat NA is unlikely to be successful unless there were technical difficulties such as a blocked or kinked catheter. There is some limited evidence that VATS is the preferred 'salvage' strategy after failed NA,[98] but this is not the usual practice currently in the UK where small-bore chest drain insertion is usually employed. Following successful NA, the patient can be considered for hospital discharge.

Suction

- **Suction should not be routinely employed. (B)**
- **Caution is required because of the risk of RPO. (B)**
- **High-volume low-pressure suction systems are recommended. (C)**

A persistent air leak with or without incomplete re-expansion of the lung is the usual reason for consideration of the use of suction, although there is no evidence for its routine use.[99–101] It is arbitrarily defined as the continued bubbling of air through a chest drain after 48 h in situ. A retrospective review of 142 cases of pneumothorax[102] found a median time to resolution of 8 days which was not related to the initial size of pneumothorax, but longer for SSP. A persistent air leak was observed in 43 cases, 30 of which were treated with suction. The theory that underpins the role of suction is that air might be removed from the pleural cavity at a rate that exceeds the egress of air through the breach in the visceral pleura and to subsequently promote healing by apposition of the visceral and parietal pleural layers. It has been suggested that optimal suction should entail pressures of −10 to −20 cm H_2O (compared with normal intrapleural pressures of between −3.4 and −8 cm H_2O, according to the respiratory cycle), with the capacity to increase the air flow volume to 15–20 l/min.[103] Other forms of suction are not recommended. High-pressure high-volume suction may lead to air stealing, hypoxaemia or the perpetuation of air leaks.[104] Likewise, high-pressure low-volume systems should be avoided.[105] High-volume low-pressure systems such as Vernon-Thompson pumps or wall suction with low pressure adaptors are therefore recommended.

The addition of suction too early after chest drain insertion may precipitate RPO, especially in the case of a PSP that may have been present for more than a few days,[106] and is thought to be due to the additional mechanical stress applied to capillaries that are already 'leaky'.[107] The clinical manifestations are cough, breathlessness and chest tightness after chest drain insertion. The incidence may be up to 14% (higher in younger patients with a large PSP), although no more than a radiological phenomenon in the majority of cases.[106] Sometimes pulmonary oedema is evident in the contralateral lung.[108] Fatalities have been reported in as many as 20% of 53 cases in one series,[108] so caution should be exercised in this particular group of patients.

Specialist referral

- **Referral to a respiratory physician should be made within 24 h of admission. (C)**
- **Complex drain management is best effected in areas where specialist medical and nursing expertise is available. (D)**

Failure of a pneumothorax to re-expand or a persistent air leak should prompt early referral to a respiratory physician, preferably within the first 24 h. Such patients may require prolonged chest drainage with complex drain management (suction, chest drain repositioning) and liaison with thoracic surgeons. Drain management is also best delivered by nurses with specialist expertise. Surgical referral is discussed in a later section.

Surgical emphysema

This is a well-recognised complication of chest drainage.[109] Generally it is of cosmetic importance only, although alarming for patients and their relatives, and subsides spontaneously after a few days. It is usually seen in the context of a malpositioned, kinked, blocked or clamped chest drain. It can also occur with an imbalance between a large air leak and a relatively small-bore chest drain. Occasionally, acute airway obstruction or thoracic compression may lead to respiratory compromise[109 110] in which case tracheostomy, skin incision decompression and insertion of large-bore chest drains have all been used.[109] For most, the treatment is conservative.

Management of SSP

- **All patients with SSP should be admitted to hospital for at least 24 h and receive supplemental oxygen in**

compliance with the BTS guidelines on the use of oxygen. (D)

- **Most patients will require the insertion of a small-bore chest drain. (B)**
- **All patients will require early referral to a chest physician. (D)**
- **Those with a persistent air leak should be discussed with a thoracic surgeon at 48 h. (B)**

As stated previously, SSP is less likely to be tolerated by patients than PSP because of co-existing lung disease. Furthermore, the air leak is less likely to settle spontaneously,[111 112] so that most patients will require active intervention. Oxygen is indicated,[56 57] but caution is required for patients with carbon dioxide retention.[113] Aspiration is less likely to be successful in SSP (see evidence table available on the BTS website at www.brit-thoracic.org.uk) but can be considered in symptomatic patients with small pneumothoraces in an attempt to avoid chest drain insertion. Otherwise, the insertion of a small-bore chest drain is recommended, a study in SSP[114] having found equivalent success to the use of large drains. Early referral to a chest physician is encouraged for all patients with SSP, both for management of the pneumothorax and also of the underlying lung disease. Similarly, those with a persistent air leak should be discussed with a thoracic surgeon after 48 h,[112 115] even though many will resolve spontaneously if managed conservatively for as long as 14 days.[111]

Patients with SSP but unfit for surgery

- **Medical pleurodesis may be appropriate for inoperable patients. (D)**
- **Patients with SSP can be considered for ambulatory management with a Heimlich valve. (D)**

These patients are at heightened risk of a persistent air leak but may not be fit for surgical intervention by virtue of the severity of their underlying lung disease, or they may be unwilling to proceed. Their optimal management is challenging and requires close medical and surgical liaison. Medical pleurodesis is an option for such patients, as is ambulatory management with the use of a Heimlich valve.[86]

DISCHARGE AND FOLLOW-UP

- **Patients should be advised to return to hospital if increasing breathlessness develops. (D)**
- **All patients should be followed up by respiratory physicians until full resolution. (D)**
- **Air travel should be avoided until full resolution. (C)**
- **Diving should be permanently avoided unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and chest CT scan postoperatively. (C)**

All patients discharged after active treatment or otherwise should be given verbal and written advice to return to the Accident and Emergency department immediately should they develop further breathlessness. It is recommended that all patients should be followed up by a respiratory physician to ensure resolution of the pneumothorax, to institute optimal care of any underlying lung disease, to explain the risk of recurrence and the possible later need for surgical intervention and to reinforce lifestyle advice on issues such as smoking and air travel. Those managed by observation alone or by NA should be advised to return for a follow-up chest x-ray after 2–4 weeks to monitor resolution. Those with successful lung re-expansion before hospital discharge will also require early review because recurrence may occur relatively early.

Since there is no evidence to link recurrence with physical exertion, the patient can be advised to return to work and to resume normal physical activities once all symptoms have resolved, although it is reasonable to advise that sports that involve extreme exertion and physical contact should be deferred until full resolution. Patients should be made aware of the danger of air travel in the presence of a current closed pneumothorax, and should be cautioned against commercial flights at high altitude until full resolution of the pneumothorax has been confirmed by a chest x-ray. While there is no evidence that air travel per se precipitates pneumothorax recurrence, the consequences of a recurrence during air travel may be serious. Many commercial airlines previously advised arbitrarily a 6-week interval between the pneumothorax event and air travel, but this has since been amended to a period of 1 week after full resolution. The BTS guidelines on air travel[116] emphasise that the recurrence risk only significantly falls after a period of 1 year from the index pneumothorax so that, in the absence of a definitive surgical procedure, patients with SSP in particular may decide to minimise the risk by deferring air travel accordingly. After a pneumothorax, diving should be discouraged permanently[117] unless a very secure definitive prevention strategy has been performed such as surgical pleurectomy. The BTS guidelines on respiratory aspects of fitness for diving[118] deal with this in greater detail. Smoking influences the risk of recurrence,[12 15] so cessation should be advised. Pregnancy is an issue to be discussed with younger female patients.

MEDICAL CHEMICAL PLEURODESIS

- **Chemical pleurodesis can control difficult or recurrent pneumothoraces (A) but, since surgical options are more effective, it should only be used if a patient is either unwilling or unable to undergo surgery. (B)**
- **Chemical pleurodesis for pneumothorax should only be performed by a respiratory specialist. (C)**

Chemical pleurodesis has generally been advocated by respiratory physicians experienced in thoracoscopy. The instillation of substances into the pleural space should lead to an aseptic inflammation, with dense adhesions leading ultimately to pleural symphysis. There is a significant rate of recurrence of both primary and secondary pneumothoraces,[12] and efforts to reduce recurrence by instilling various sclerosants—either via a chest drain, video-assisted thoracoscopic surgery (VATS) or open surgery—are often undertaken without clear guidelines to direct physicians in their use. In the vast majority of cases the prevention of recurrent pneumothoraces should be undertaken surgically using either an open or VATS approach, as the rate of recurrence following surgical pleurodesis via thoracotomy or VATS is far less than following simple medical pleurodesis with chemical agents,[32 119–121] although direct comparative trials are lacking. A small number of patients are either too frail or are unwilling to undergo any surgical treatment and, in these situations, medical chemical pleurodesis may be appropriate.

Many sclerosing agents suitable for instillation into the pleural space have been studied.[32 119 122–125] Tetracycline used to be recommended as the first-line sclerosant therapy for both primary and secondary pneumothoraces as it proved to be the most effective sclerosant in animal models.[123 126 127] Recently, however, parenteral tetracycline for pleurodesis has become more difficult to obtain owing to problems with the manufacturing process. Minocycline and doxycycline have also been shown to be reasonable alternative sclerosing agents in animal models.[126 127]

The rate of recurrence of pneumothorax is the primary indicator for success for any recurrence prevention techniques. Although tetracycline has been shown to reduce the incidence of early recurrence, the incidence of late recurrence remains at 10–20% which is unacceptably high when compared with surgical methods of pleurodesis.[119 121 125 128 129] Tetracycline can be recommended for recurrent primary and secondary pneumothorax when surgery is not an option, and graded talc may also be used on the grounds that it is the most effective agent in treating malignant pleural effusion and is also commonly used for surgical chemical pleurodesis.[130–133] There is conflicting evidence as to whether tetracycline is effective for the treatment of a fully expanded pneumothorax with a persistent air leak.[32 134 135] The largest of these studies, the Veterans Administration Study, did not support the use of intrapleural tetracycline to facilitate the closure of a persistent air leak.[31] Macoviak and colleagues[135] suggest that intrapleural tetracycline can facilitate the closure of a persistent air leak provided the lung can be kept expanded so that symphysis can occur. Likewise, there is conflicting evidence as to whether intrapleural tetracycline shortens the length of stay in hospital with pneumothorax.[32 119 125]

The dosage of intrapleural tetracycline requires clarification. Almind[119] found a reduction in the recurrence rate in a group receiving 500 mg tetracycline via chest drains compared with those treated by tube drainage alone. This reduction was not significant. The Veterans Administration Study,[32] which used 1500 mg tetracycline, showed a significant reduction in the recurrence rate of pneumothorax without significant extra morbidity. This dose of intrapleural tetracycline is therefore recommended as the standard dose for medical pleurodesis. While pain was reported more frequently in the group treated with tetracycline at a dose of 1500 mg,[32] others have reported no increase in pain with doses of 500 mg provided adequate analgesia is given.[119] Adequate analgesia may be achieved with the administration of intrapleural local anaesthesia. Standard doses (200 mg (20 ml) of 1% lidocaine) are significantly less effective than larger doses (250 mg (25 ml) of 1% lidocaine), the higher doses having been shown to increase the number of pain-free episodes from 10% to 70% with no appreciable toxicity.[136]

Chemical pleurodesis using graded talc is an effective alternative to tetracycline pleurodesis, but there are no controlled trials comparing the two in the treatment of pneumothorax. The issue of talc pleurodesis is discussed in the later section on surgical chemical pleurodesis as most trials using talc relate to its use in either thoracoscopic or open surgical techniques. Since we recognise chemical pleurodesis as an inferior option to surgical pleurodesis, we recommend that chemical pleurodesis should be undertaken by respiratory physicians or thoracic surgeons only.

REFERRAL TO THORACIC SURGEONS

- **In cases of persistent air leak or failure of the lung to re-expand, an early (3–5 days) thoracic surgical opinion should be sought. (C)**

There is no evidence on which to base the ideal timing for thoracic surgical intervention in cases of persistent air leak. A cut-off point of 5 days has been widely advocated in the past[55] but is arbitrary. Chee *et al*[111] showed that 100% of primary pneumothoraces with a persistent air leak for >7 days and treated by tube drainage had resolved by 14 days. Also, 79% of those with secondary pneumothoraces and a persistent air leak had resolved by 14 days, with no mortality in either group. However, surgical intervention carries a low morbidity[128 129 137–140] and post-surgical recurrence rates are low.[128 129] Surgical intervention as early as 3 days has advocates,[141 142] but there is no evidence that intervention before 5 days is necessary for PSP. Each case should be assessed individually on its own merit. Patients with pneumothoraces should be managed by a respiratory physician, and a thoracic surgical opinion will often form an early part of the management plan.

Accepted indications for surgical advice should be as follows:

- Second ipsilateral pneumothorax.
- First contralateral pneumothorax.
- Synchronous bilateral spontaneous pneumothorax.
- Persistent air leak (despite 5–7 days of chest tube drainage) or failure of lung re-expansion.
- Spontaneous haemothorax.[143 144]
- Professions at risk (eg, pilots, divers).[111 138 145–147]
- Pregnancy.

Increasingly, patient choice will play a part in decision-making, and even those without an increased risk in the event of a pneumothorax because of their profession may elect to undergo surgical repair after their first pneumothorax,[148 149] weighing the benefits of a reduced recurrence risk against that of chronic pain,[150] paraesthesia[151] or the possibility of increased costs.[152]

Surgical strategies: open thoracotomy or VATS?

- **Open thoracotomy and pleurectomy remain the procedure with the lowest recurrence rate (approximately 1%) for difficult or recurrent pneumothoraces. (A)**
- **Video-assisted thoracoscopic surgery (VATS) with pleurectomy and pleural abrasion is better tolerated but has a higher recurrence rate of approximately 5%. (A)**

There are two main objectives in the surgical repair of persistent air leak from a pneumothorax and in the prevention of recurrence. The first objective is to resect any visible bullae or blebs on the visceral pleura and also to obliterate emphysema-like changes[9] or pleural porosities under the surface of the visceral pleura.[8] The second objective is to create a symphysis between the two opposing pleural surfaces as an additional means of preventing recurrence. In the past, surgeons have tended to favour a surgical pleurodesis with pleural abrasion while others have stressed the importance of various degrees of pleurectomy in recurrence prevention.[137 153 154] Although there may be slight advantages of pleurectomy over pleural abrasion,[137] a combination of the two is often used.[155–158] Unfortunately there is a paucity of good comparative case-controlled studies in this area.[128 129] In recent years, less invasive procedures using VATS have become more popular with lower morbidity although with slightly higher recurrence rates.

Open thoracotomy with pleural abrasion was the original surgical treatment for pneumothorax, described by Tyson and Crandall in 1941.[159] In 1956 Gaensler introduced parietal pleurectomy for recurrent pneumothoraces, encouraging pleural symphysis through adhesions between the visceral pleura and the chest wall.[153] Closure of the leaking visceral pleura with direct cautery and ligation or suture of associated blebs[147] is also thought to be important. Although open thoracotomy has the lowest pneumothorax recurrence rates, there are also lesser surgical procedures with comparable recurrence rates but less morbidity.[160] These include trans-axillary minithoracotomy, using a 5–6 cm incision in the axillary margin with apical pleurectomy and pleural abrasion, introduced in the 1970s.[161] Open thoracotomy is generally performed with a limited posterolateral approach and single lung ventilation. This allows for a parietal pleurectomy with excision, stapling or ligation of visible bullae and pleural abrasion.[162] Isolated lung ventilation during open thoracotomy

renders easier visualisation of the visceral pleura than during a VATS procedure.[163–165] Meta-analyses of studies comparing open with limited or VATS procedures[128 129] have shown lower recurrence rates (approximately 1%) with open procedures but greater blood loss, more postoperative pain[166] and longer hospital stays.[167] Some non-randomised studies have found no significant differences.[168 169] A complicated meta-analysis of three retrospective studies and one prospective study comparing the cost of open thoracotomy versus VATS (not exclusively for pneumothoraces) concluded that the total economic cost of VATS was lower,[170] and it can be undertaken without general anaesthesia.[149] There is a need for better quality prospective randomised studies in this area. Several authors suggest that VATS offers a significant advantage over open thoracotomy, including a shorter postoperative hospital stay,[145 162 167 171–173] less postoperative pain[160 162 166 174 175] and improved pulmonary gas exchange postoperatively,[176] although not all trials have confirmed shorter hospital stays with VATS.[169 177]

Much of the literature contains heterogeneous comparisons between PSP and SSP, but the most recent 'clinical bottom line'[129] concludes that VATS pleurectomy is comparable to open pleurectomy, with several randomised controlled trials showing reductions in length of hospital stay, analgesic requirement and postoperative pulmonary dysfunction. Clearly this needs to be weighed against the slight increase in recurrence rate when using a less invasive approach.[128]

Surgical chemical pleurodesis

- **Surgical chemical pleurodesis is best achieved by using 5 g sterile graded talc, with which the complications of adult respiratory distress syndrome and empyema are rare. (A)**

With the advent of VATS for pneumothorax repair and recurrence prevention, the use of surgical chemical pleurodesis has declined significantly. Previous reports have shown that talc can achieve pleurodesis successfully in 85–90% of cases, similar to other thoracoscopic techniques for complicated pneumothorax.[121 145 171 178 179] A meta-analysis of the success rates of talc pleurodesis in the treatment of pneumothorax shows an overall success rate of 91%.[178] Graded talc is preferable to tetracycline, which is less available now, and is associated with much higher recurrence rates.[120] Much of the literature concerning the use of talc in achieving pleurodesis relates to its use in the control of malignant pleural effusions, although talc poudrage has been used successfully in secondary pneumothoraces.[180] On the basis of a systematic review of uncontrolled trials, 5 g of intrapleural talc via VATS achieves a success rate of 87%.[178]

The adult respiratory distress syndrome has been described following the use of talc. This probably relates to the size of the talc particles[181] and is unlikely to occur with the use of graded talc.[182 183] If talc is correctly sterilised, the incidence of empyema is very low.[178 184 185] There does not appear to be a difference between talc poudrage and talc slurry pleurodesis. The advent of successful and well-tolerated VATS surgery will lead to less use of surgical chemical pleurodesis with talc. In those patients who are either unwilling or too unwell to undergo a VATS procedure, then medical pleurodesis with talc via a chest drain would be the preferred option.

TENSION PNEUMOTHORAX

- **Tension pneumothorax is a medical emergency that requires heightened awareness in a specific range of clinical situations. (D)**
- **Treatment is with oxygen and emergency needle decompression. (D)**
- **A standard cannula may be insufficiently long if used in the second intercostal space. (D)**

This is a medical emergency that can arise in a variety of clinical situations, so a high index of suspicion is required in order to make the correct diagnosis and to manage it effectively. The most frequent situations are shown in box 1, although the list does not include all eventualities. It arises as a result of the development of a one-way valve system at the site of the breach in the pleural membrane, permitting air to enter the pleural cavity during inspiration but preventing egress of air during expiration, with consequent increase in the intrapleural pressure such that it exceeds atmospheric pressure for much of the respiratory cycle. As a result, impaired venous return and reduced cardiac output results in the typical features of hypoxaemia and haemodynamic compromise.[186 187]

A recent review[188] has emphasised the important differences between the presentation in ventilated and non-ventilated patients, where it is typically seen after trauma or resuscitation. The former group is associated with a uniformly rapid presentation with hypotension, tachycardia, falling oxygen saturation and cardiac output, increased inflation pressures and cardiac arrest. This is frequently missed in the ICU setting[37] and can also occur after nasal non-invasive ventilation (NIV). The latter group of awake patients show a greater variability of presentations which are generally progressive with slower decompensation. Tachypnoea, tachycardia and hypoxaemia lead eventually to respiratory arrest. Apart from these general physical signs, the most frequent lateralising sign found in a review of 18 case reports[188] was that of decreased air entry (50–75%), with signs of tracheal deviation, hyperexpansion, hypomobility and hyperresonance present only in the minority.

In neither group is imaging especially helpful; there is usually insufficient time to obtain a chest x-ray and, even if available, the size of the pneumothorax or the presence of mediastinal displacement correlate poorly with the presence of tension within a pneumothorax. However, a chest x-ray can, when time is available, confirm the presence of a pneumothorax (if uncertain) and the correct side.

Treatment is with high concentration oxygen and emergency needle decompression, a cannula usually being introduced in the second anterior intercostal space in the mid-clavicular line. The instantaneous egress of air through the majority of the respiratory cycle is an important confirmation of the diagnosis and the correct lateralisation. A standard 14 gauge (4.5 cm) cannula may not be long enough to penetrate the parietal pleura, however, with up to one-third of patients having a chest wall thickness

Box 1 Typical clinical situations where tension pneumothorax arises

1. Ventilated patients on ICU.
2. Trauma patients.
3. Resuscitation patients (CPR).
4. Lung disease, especially acute presentations of asthma and chronic obstructive pulmonary disease.
5. Blocked, clamped or displaced chest drains.
6. Patients receiving non-invasive ventilation (NIV).
7. Miscellaneous group, for example patients undergoing hyperbaric oxygen treatment.

>5 cm in the second interspace.[189] The chest wall may be less deep in the fourth or fifth interspace, and this could provide an alternative site for decompression or a chest drain may need to be inserted if there is an initial treatment failure. In any case, a chest drain should be inserted immediately after needle decompression and the cannula left in place until bubbling is confirmed in the underwater seal system to confirm proper function of the chest drain.[186]

PNEUMOTHORAX AND PREGNANCY

- **Pneumothorax recurrence is more common in pregnancy, poses risks to the mother and fetus, and requires close cooperation between chest physicians, obstetricians and thoracic surgeons. (C)**
- **The modern and less invasive strategies of simple observation and aspiration are usually effective during pregnancy, with elective assisted delivery and regional anaesthesia at or near term. (C)**
- **A corrective surgical procedure (VATS) should be considered after delivery. (D)**

Although less common in women than in men, the occurrence of PSP in women of childbearing age is not unusual. There appears to be an increased risk of recurrence during pregnancy and during parturition,[190] with potential risks to the mother and fetus. The earlier literature consists largely of case reports and described varied and relatively invasive management strategies such as prolonged intrapartum chest tube drainage, intrapartum thoracotomy, premature induction of labour or caesarean section. A more recent case series and literature review[191] has recommended the use of more modern conservative management methods for which favourable outcomes have now been experienced. Pneumothorax that occurs during pregnancy can be managed by simple observation if the mother is not dyspnoeic, there is no fetal distress and the pneumothorax is small (<2 cm). Otherwise aspiration can be performed, chest drain insertion being reserved for those with a persistent air leak.

Close cooperation between the respiratory physician, obstetrician and thoracic surgeon is essential. To avoid spontaneous delivery or caesarean section, both of which have been associated with an increased risk of recurrence, the safest approach will usually be that of elective assisted delivery (forceps or ventouse extraction) at or near term, with regional (epidural) anaesthesia. Less maternal effort is required with forceps delivery, which is therefore preferable. If caesarean section is unavoidable because of obstetric considerations, then a spinal anaesthetic is preferable to a general anaesthetic.

Because of the risk of recurrence in subsequent pregnancies, a minimally invasive VATS surgical procedure should be considered after convalescence. Successful pregnancies and spontaneous deliveries without pneumothorax recurrence have been reported after a VATS procedure.[191]

CATAMENIAL PNEUMOTHORAX

- **Catamenial pneumothorax is underdiagnosed in women with pneumothorax. (C)**
- **A combination of surgical intervention and hormonal manipulation requires cooperation with thoracic surgeons and gynaecologists. (D)**

Catamenial is a term that derives from the Greek meaning 'monthly'. The typical combination of chest pain, dyspnoea and haemoptysis occurring within 72 h before or after menstruation in young women has been thought to be relatively rare. There are approximately 250 cases described in the medical literature,[192] but it is likely that the majority of cases are not reported. Most of these references are of solitary case reports or small series. The associated pneumothorax is usually right-sided and there is a heightened tendency to recurrence coinciding with the menstrual cycle. Many cases have evidence of pelvic endometriosis. Although the aetiology is not fully understood, inspection of the pleural diaphragmatic surface at thoracoscopy often reveals defects (termed fenestrations) as well as small endometrial deposits. These deposits have also been seen on the visceral pleural surface. Among women undergoing routine surgical treatment for recurrent pneumothorax, however, catamenial pneumothorax has been diagnosed in as many as 25%.[193] Thus, it may be relatively underdiagnosed.

Extragenital or 'ectopic' endometriosis is an uncommon condition that can affect almost any organ system and tissue within the body, the thorax being the most frequent extrapelvic location. What has been termed the thoracic endometriosis syndrome (TES) includes catamenial pneumothorax, catamenial haemothorax, catamenial haemoptysis and lung nodules (purple or brown coloured). The most accepted theory to explain the phenomenon of catamenial pneumothorax is that of aspiration of air from the abdomen and genital tract via the diaphragmatic fenestrations, but the appearance of endometriosis deposits on the visceral pleural surface raises the possibility that erosion of the visceral pleura might be an alternative mechanism. Haemoptysis is thought to result from intrapulmonary endometriosis deposits, the mechanism by which endometrial tissue reaches the lung being poorly understood.

The management strategies can be divided into thoracic surgical techniques and hormonal manipulation although, in the past, total abdominal hysterectomy and bilateral salpingohysterectomy have been employed. Thoracic surgical techniques have been varied and include diaphragmatic resection or plication of the fenestrations seen at thoracoscopy, the insertion of a mesh or patch over these fenestrations, electrocoagulation of the endometriosis deposits and pleurodesis. This variability reflects the general lack of success with surgical intervention alone, recurrence rates of up to 30% being documented.[194] When combined with gonadotrophin-releasing hormone analogues amenorrhoea results, but recurrence has been avoided with follow-up approaching periods of 4 years.[195] Successful patient management requires close cooperation between respiratory physicians, thoracic surgeons and gynaecologists.

PNEUMOTHORAX AND AIDS

- **The combination of pneumothorax and HIV infection requires early intercostal tube drainage and surgical referral, in addition to appropriate treatment for HIV and PJP infection. (C)**

Over the course of the last 20 years a strong association has been observed between HIV infection and pneumothorax. Historically, up to 5% of AIDS patients developed pneumothorax[196–198] and up to 25% of spontaneous pneumothoraces occurred in HIV-infected patients in large urban settings where a high prevalence occurred.[27 28 199] *Pneumocystis jiroveci* (PJP)—previously known as *Pneumocystis carinii* (PCP)—infection has been considered to be the main aetiological factor for this association, because of a severe form of necrotising alveolitis that occurs in which the subpleural pulmonary parenchyma is replaced by necrotic thin-walled cysts and pneumatoceles.[200 201] The administration of nebulised pentamidine has also been suggested as a possible independent risk factor.[196] The use of systemic corticosteroids may also contribute to the morbidity in such patients.[202]

Due to the histopathology outlined above, pneumothoraces caused by PJP have a tendency to more prolonged air leaks, treatment failure, recurrence and higher hospital mortality.[203] Up to 40% of these patients can develop bilateral pneumothorax. Treatment failures have been observed to correlate with the degree of immunosuppression, as reflected by CD4 counts.[203] In view of these features, management strategies have been evolved that incorporate early and aggressive intervention including tube drainage, pleurodesis and surgical techniques such as pleurectomy.[197 199 202–205] Observation and simple aspiration are not likely to suffice, even in the first instance.

Over the last 5 years, and since the last BTS guidelines, the global spectrum of HIV infection has changed significantly as a result of the more widespread use of both antiretroviral therapy and PJP prophylaxis. While the disease burden remains very high in the underdeveloped world, the prognosis for such patients in Western societies has greatly improved,[206] where this combination is now much less frequently encountered. As HIV is now becoming a more chronic disease associated with a high incidence of smoking and therefore of COPD, pneumothoraces might become more significant when they occur.

However, the mortality of patients who require intensive care for PJP in HIV infection remains high, especially when pneumothorax occurs during ventilation. Although antiretroviral therapy that is commenced before or during hospitalisation can improve the outcome,[207] the potential risk of the 'immune reconstitution syndrome' has to be taken into consideration.

PNEUMOTHORAX AND CYSTIC FIBROSIS

- **The development of a pneumothorax in a patient with cystic fibrosis requires early and aggressive treatment with early surgical referral. (C)**
- **Pleural procedures, including pleurodesis, do not have a significant adverse effect on the outcome of subsequent lung transplantation. (D)**

Even though long-term survival has improved significantly, spontaneous pneumothorax remains a common complication of cystic fibrosis, occurring in 0.64% of patients per annum and 3.4% of patients overall.[208] It occurs more commonly in older patients and those with more advanced lung disease, and is associated with a poor prognosis, the median survival being 30 months.[209] Contralateral pneumothoraces occur in up to 40% of patients.[209 210] An increased morbidity also results, with increased hospitalisation and a measurable decline in lung function.[208] While a small pneumothorax without symptoms can be observed or aspirated, larger pneumothoraces require a chest drain. The collapsed lung can be stiff and associated with sputum retention, thus requiring a longer time to re-expand. During this time other general measures, such as appropriate antibiotic treatment, are needed.

Chest tube drainage alone has a recurrence rate of 50%, but interventions such as pleurectomy, pleural abrasion and pleurodesis have lower rates.[211–213] With a success rate of 95% and with little associated reduction in pulmonary function, partial pleurectomy is generally regarded as the treatment of choice in patients with cystic fibrosis and recurrent pneumothoraces who are fit to undergo surgery.[209] In those who are not fit for surgery and in whom re-expansion may take several weeks with a chest drain and suction, pleurodesis offers an alternative strategy.[209] This had been thought to be a relative contraindication to later transplantation because of the need for a lengthier transplant procedure and excessive bleeding.[214] A more recent study[215] has concluded that previous pleural procedures should not be considered as a contraindication for transplantation, there being no significant effect on surgical outcome although more dense pleural adhesions were observed than in a control population.

IATROGENIC PNEUMOTHORAX

Iatrogenic pneumothorax has been shown to be even more common than spontaneous pneumothorax in several large reviews,[216 217] the most common causes being transthoracic needle aspiration (24%), subclavian vessel puncture (22%), thoracocentesis (22%), pleural biopsy (8%) and mechanical ventilation (7%).[218] It is also a complication of transbronchial biopsy. During transthoracic needle aspiration the two primary risk factors are the depth of the lesion and the presence of COPD.[219] A large retrospective survey in the USA found an incidence of 2.68% among patients undergoing thoracocentesis.[220] No means of reducing this risk has yet been identified. Positioning of the patient so that the procedure is performed in a dependent area has had no beneficial effect.[221] Excluding iatrogenic penumothorax that occurs in intensive care units, the treatment seems to be relatively simple with less likelihood of recurrence (the underlying risk factors for SP not usually being present). The majority resolve spontaneously by observation alone. If intervention is required, simple aspiration has been shown to be effective in 89% of patients.[94] For the remainder a chest drain is required, this being more likely in patients with COPD.[222]

In the intensive care unit iatrogenic pneumothorax is a life-threatening complication that may be seen in up to 3% of patients.[223] Those on positive pressure ventilation require chest drain insertion as positive pressure maintains the air leak.[224]

CONCLUDING REMARKS

These pneumothorax guidelines differ from the last (2003) BTS guidelines in that they have been produced in accordance with the SIGN methodology and therefore have necessitated a careful analysis of the current underlying evidence. Unfortunately there are relatively few adequate studies that address the main areas of uncertainty, and few additions to the knowledge base in the last 7 years. Nevertheless, some subtle changes in practice have occurred. These are incorporated, together with coverage of some additional topics of relevance such as catamenial pneumothorax and the issue of pneumothorax in pregnancy. The treatment algorithm is now illustrated on a single flowchart for both PSP and SSP and places slightly less emphasis on the size of the pneumothorax and more on the clinical features. However, the trend towards more conservative management is maintained, with observation for many patients with PSP, aspiration for the remainder, and small-bore chest drains for persistent air leaks. The imaging of pneumothorax has undergone a major change due to the advent of PACS technology, and the implications of this are now described. Surgical practice has also developed with the widespread adoption of less invasive (VATS) procedures rather than open thoracotomies. While the challenge of pneumothorax management in patients with cystic fibrosis remains, there has been a significant reduction in pneumothorax in patients with HIV since the introduction of antiretroviral therapy and PJP prophylactic therapy, in the countries with advanced healthcare systems at least. It is hoped that these guidelines build upon their predecessors and lead to improved care for patients with pneumothorax, and that they inform and support the clinicians who care for them.

Competing interests No member of the Guideline Group is aware of any competing interests.

Provenance and peer review The draft guideline was available for online public consultation (July/August 2009) and presented to the BTS Winter Meeting (December 2009). Feedback was invited from a range of stakeholder institutions (see

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Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010

Mark E Roberts,[1] Edmund Neville,[2] Richard G Berrisford,[3] George Antunes,[4] Nabeel J Ali[1], on behalf of the BTS Pleural Disease Guideline Group

[1]Sherwood Forest Hospitals NHS Foundation Trust, UK
[2]Portsmouth Hospitals NHS Trust, UK
[3]Royal Devon and Exeter NHS Trust, UK
[4]South Tees NHS Foundation Trust, UK

Correspondence to
Dr Nabeel J Ali, Sherwood Forest Hospitals NHS Foundation Trust, Kingsmill Hospital, Mansfield Road, Sutton in Ashfield NG17 4JL, UK;
nabeel.ali@sfh-tr.nhs.uk

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INTRODUCTION

The discovery of malignant cells in pleural fluid and/or parietal pleura signifies disseminated or advanced disease and a reduced life expectancy in patients with cancer.[1] Median survival following diagnosis ranges from 3 to 12 months and is dependent on the stage and type of the underlying malignancy. The shortest survival time is observed in malignant effusions secondary to lung cancer and the longest in ovarian cancer, while malignant effusions due to an unknown primary have an intermediate survival time.[2–6] Historically, studies showed that median survival times in effusions due to carcinoma of the breast are 5–6 months. However, more recent studies have suggested longer survival times of up to 15 months.[7–10] A comparison of survival times in breast cancer effusions in published studies to 1994 calculated a median survival of 11 months.[9]

Currently, lung cancer is the most common metastatic tumour to the pleura in men and breast cancer in women.[4 11] Together, both malignancies account for 50–65% of all malignant effusions (table 1). Lymphomas, tumours of the genitourinary tract and gastrointestinal tract account for a further 25%.[2 12–14] Pleural effusions from an unknown primary are responsible for 7–15% of all malignant pleural effusions.[3 13 14] Few studies have estimated the proportion of pleural effusions due to mesothelioma: studies from 1975, 1985 and 1987 identified mesothelioma in 1/271, 3/472 and 22/592 patients, respectively, but there are no more recent data to update this in light of the increasing incidence of mesothelioma.[4 13 14]

Attempts have been made to predict survival based on the clinical characteristics of pleural fluid. None has shown a definite correlation: a recent systematic review of studies including 433 patients assessing the predictive value of pH concluded that low pH does not reliably predict a survival of <3 months.[15 16] In malignant mesothelioma, one study has shown an association between increasing pH and increasing survival.[17] Burrows *et al* showed that only performance status was significantly associated with mortality: median survival was 1.1 months with a Karnofsky score <30 and 13.2 months with a score >70.[18]

An algorithm for the management of malignant pleural effusions is shown in figure 1.

CLINICAL PRESENTATION

- **The majority of malignant effusions are symptomatic. (C)**
- **Massive pleural effusions are most commonly due to malignancy. (C)**

The majority of patients who present with a malignant pleural effusion are symptomatic, although up to 25% are asymptomatic with an incidental finding of effusion on physical examination or by chest radiography.[1] Dyspnoea is the most common presenting symptom, reflecting reduced compliance of the chest wall, depression of the ipsilateral diaphragm, mediastinal shift and reduction in lung volume.[19] Chest pain is less common and is usually related to malignant involvement of the parietal pleura, ribs and other intercostal structures. Constitutional symptoms including weight loss, malaise and anorexia generally accompany respiratory symptoms.

A massive pleural effusion is defined as complete or almost complete opacification of a hemithorax on the chest x-ray. It is usually symptomatic and is commonly associated with a malignant cause.[20] The diagnosis of a malignant pleural effusion is discussed in the guideline on the investigation of a unilateral pleural effusion.

MANAGEMENT OPTIONS

Treatment options for malignant pleural effusions are determined by several factors: symptoms and performance status of the patient, the primary tumour type and its response to systemic therapy, and degree of lung re-expansion following pleural fluid evacuation. Although small cell lung cancer, lymphoma and breast cancer usually respond to chemotherapy, associated secondary pleural effusions may require intervention during the course of treatment (figure 1). Malignant pleural effusions are often most effectively managed by complete drainage of the effusion and instillation of a sclerosant to promote pleurodesis and prevent recurrence of the effusion. Options for management include observation, therapeutic pleural aspiration, intercostal tube drainage and instillation of sclerosant, thoracoscopy and pleurodesis or placement of an indwelling pleural catheter.

Observation

- **Observation is recommended if the patient is asymptomatic and the tumour type is known. (C)**
- **Advice should be sought from the respiratory team and/or respiratory multidisciplinary team for symptomatic malignant effusions. (✓)**

The majority of these patients will become symptomatic in due course and require further intervention. There is no evidence that initial thoracentesis carried out according to standard techniques will

Table 1 Primary tumour site in patients with malignant pleural effusion

Primary tumour site	Salyer[14] (n=95)	Chernow[1] (n=96)	Johnston[13] (n=472)	Sears[4] (n=592)	Hsu[12] (n=785)	Total (%)
Lung	42	32	168	112	410	764 (37.5)
Breast	11	20	70	141	101	343 (16.8)
Lymphoma	11	—	75	92	56	234 (11.5)
Gastrointestinal	—	13	28	32	68	141 (6.9)
Genitourinary	—	13	57	51	70	191 (9.4)
Other	14	5	26	88	15	148 (7.8)
Unknown primary	17	13	48	76	65	219 (10.7)

reduce the chances of subsequent effective pleurodesis after tube drainage. However, repeated thoracentesis may limit the scope for thoracoscopic intervention as it often leads to the formation of adhesions between the parietal and visceral pleura.

Therapeutic pleural aspiration

- **Pleural effusions treated by aspiration alone are associated with a high rate of recurrence of effusion at 1 month so aspiration is not recommended if life expectancy is >1 month. (A)**
- **Caution should be taken if removing >1.5 l on a single occasion. (C)**

Repeated therapeutic pleural aspiration provides transient relief of symptoms and avoids hospitalisation for patients with limited survival expectancy and poor performance status. It is appropriate for frail or terminally ill patients. However, as small-bore chest tubes are widely available, effective and may be inserted with minimal discomfort,[21–26] they may be preferable. The amount of fluid evacuated by pleural aspiration will be guided by patient symptoms (cough, chest discomfort)[27] and should be limited to 1.5 l on a single occasion. Pleural aspiration alone and intercostal tube drainage without instillation of a sclerosant are associated with a high recurrence rate and a small risk of iatrogenic pneumothorax and empyema.[28–36] Therapeutic pleural aspiration should take place under ultrasound guidance (see guideline on pleural procedures).

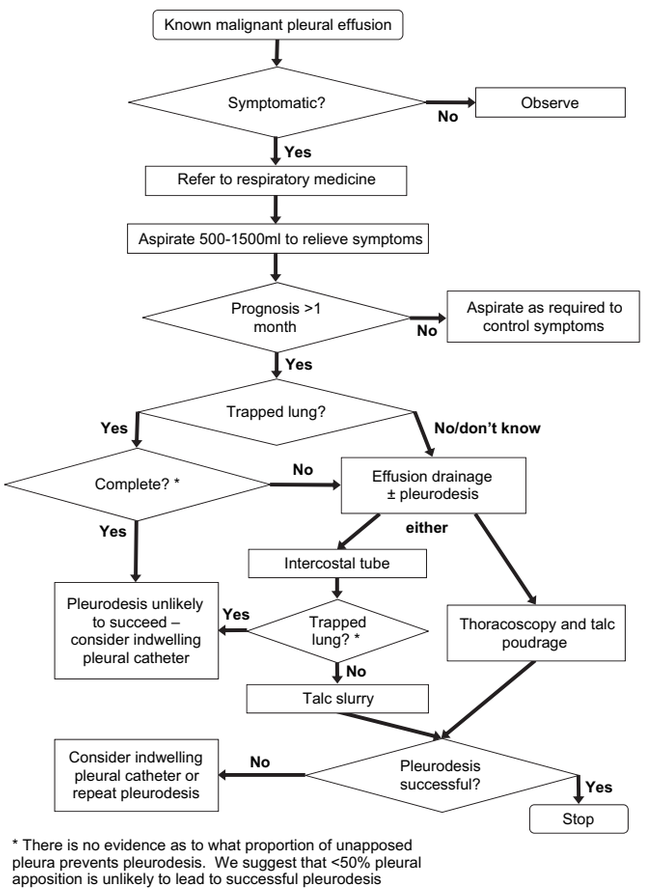

Figure 1 Management algorithm for malignant pleural effusion.

Intercostal tube drainage and intrapleural instillation of sclerosant

- **Other than in patients with a very short life expectancy, small-bore chest tubes followed by pleurodesis are preferable to recurrent aspiration. (✓)**
- **Intercostal drainage should be followed by pleurodesis to prevent recurrence unless lung is significantly trapped. (A)**

Pleurodesis is thought to occur through a diffuse inflammatory reaction and local activation of the coagulation system with fibrin deposition.[37 38] Increased pleural fibrinolytic activity is associated with failure of pleurodesis, as is extensive tumour involvement of the pleura.[39 40] Intercostal drainage without pleurodesis is associated with a high rate of effusion recurrence and should be avoided (see evidence table available on the BTS website at www.brit-thoracic.org.uk). A suggested method for undertaking pleurodesis is shown in box 1.

In animals the effectiveness of pleurodesis may be reduced by concomitant use of corticosteroids. Recent evidence in rabbits has shown reduced pleural inflammatory reaction and, in some cases, prevention of pleurodesis with administration of corticosteroids at the time of talc pleurodesis.[41] A subgroup analysis comparing the efficacy of pleurodesis in the presence and absence of non-randomised oral corticosteroid use also suggested a negative effect of corticosteroids on efficacy.[42] The administration of non-steroidal anti-inflammatory drugs (NSAIDs) at the time of pleurodesis is more contentious. Animal studies have suggested that the use of NSAIDs may impair the action of pleurodesis agents, but there is no evidence from human studies.[43]

Size of intercostal tube

- **Small-bore (10–14 F) intercostal catheters should be the initial choice for effusion drainage and pleurodesis. (A)**

Conventional large-bore intercostal tubes (24–32 F) have been employed in most studies involving sclerosing agents.[44] They have traditionally been used because they are thought to be less

Box 1 How to perform talc slurry chemical pleurodesis

- Insert small-bore intercostal tube (10–14 F).
- Controlled evacuation of pleural fluid.
- Confirm full lung re-expansion and position of intercostal tube with chest x-ray. In cases where incomplete expansion occurs, see text regarding trapped lung.
- Administer premedication prior to pleurodesis (see text).
- Instill lidocaine solution (3 mg/kg; maximum 250 mg) into pleural space followed by 4-5 g sterile graded talc in 50 ml 0.9% saline.
- Clamp tube for 1-2 h.
- Remove intercostal tube within 24-48 h.

prone to obstruction by fibrin plugs, but there is little published evidence to confirm this. The placement of large-bore tubes is perceived to be associated with significant discomfort[45] and this has led to the assessment of smaller bore tubes (10–14 F) for drainage and administration of sclerosing agents.[22 46 47] Three randomised trials investigating the difference in efficacy between small- and large-bore chest tubes all concluded that they were equivalent (see evidence table available on the BTS website at www.brit-thoracic.org.uk).[21–23] Studies using small-bore intercostal tubes with commonly used sclerosants have reported similar success rates to large-bore tubes and appear to cause less discomfort.[24–26 48] The small-bore tubes in these studies were inserted either at the patient's bedside by a physician or under radiological guidance.

Small-bore tubes have been used for ambulatory or outpatient pleurodesis. Patz and colleagues used a fluoroscopically-placed tube (10 F) connected to a closed gravity drainage bag system for this purpose.[49] Bleomycin was the preferred sclerosing agent and the pleurodesis success rate approached 80%. Ambulatory drainage is discussed further in the section on indwelling pleural catheters.

Fluid drainage, pleurodesis and trapped lung

- **Large pleural effusions should be drained in a controlled fashion to reduce the risk of re-expansion pulmonary oedema. (C)**
- **In patients where only partial pleural apposition can be achieved, chemical pleurodesis may still be attempted and may provide symptomatic relief. (B)**
- **In symptomatic cases where pleural apposition cannot be achieved ('trapped lung'), indwelling pleural catheters offer a more attractive therapeutic approach than recurrent aspiration. (✓)**
- **Once effusion drainage and lung re-expansion have been radiographically confirmed, pleurodesis should not be delayed. (B)**
- **Suction to aid pleural drainage before and after pleurodesis is usually unnecessary but, if applied, a high-volume low-pressure system is recommended. (C)**

Large pleural effusions should be drained incrementally, draining a maximum of 1.5 l on the first occasion. Any remaining fluid should be drained 1.5 l at a time at 2 h intervals, stopping if the patient develops chest discomfort, persistent cough or vasovagal symptoms. Re-expansion pulmonary oedema is a well-described serious but rare complication following rapid expansion of a collapsed lung through evacuation of large amounts of pleural fluid on a single occasion and the use of early and excessive pleural suction.[50 51] Putative pathophysiological mechanisms include reperfusion injury of the underlying hypoxic lung, increased capillary permeability and local production of neutrophil chemotactic factors such as interleukin-8.[52 53]

The most important requirement for successful pleurodesis is satisfactory apposition of the parietal and visceral pleura, confirmed radiologically.[44 54 55] Incomplete lung re-expansion may be due to a thick visceral peel ('trapped lung'), pleural loculations, proximal large airway obstruction or a persistent air leak. Most studies indicate that the lack of a response following instillation of a sclerosant is associated with incomplete lung expansion.[56] Where complete lung re-expansion or pleural apposition is not achieved, pleurodesis may still be attempted or an indwelling pleural catheter may be inserted. Robinson and colleagues reported a favourable response in 9 out of 10 patients with partial re-expansion of the lung in a study using doxycycline as a sclerosing agent.[57] The amount of trapped lung compatible with successful pleurodesis is unknown. Complete lack of pleural apposition will prevent pleurodesis: consideration of an indwelling pleural catheter is recommended in this situation. Where more than half the visceral pleura and parietal pleura are apposed, pleurodesis may be attempted although there are no studies to support this recommendation.

The amount of pleural fluid drained per day before the instillation of a sclerosant (<150 ml/day) is less relevant for successful pleurodesis than radiographic confirmation of fluid evacuation and lung re-expansion. In a randomised study, a shorter period of intercostal tube drainage and hospital stay was seen in the group in whom sclerotherapy was undertaken as soon as complete lung re-expansion was documented (majority <24 h) than in the group in whom pleurodesis was attempted only when the fluid drainage was <150 ml/day. The success rate in both groups approached 80%.[55] After sclerosant instillation, the duration of intercostal drainage appears not to affect the chances of successful pleurodesis, although the only randomised study to address this question was underpowered.[58]

Suction may rarely be required for incomplete lung expansion and a persistent air leak. When suction is applied, the use of high-volume low-pressure systems is recommended with a gradual increment in pressure to about −20 cm H_2O.

Analgesia and premedication

- **Lidocaine (3 mg/kg; maximum 250 mg) should be administered intrapleurally just prior to sclerosant administration. (B)**
- **Premedication should be considered to alleviate anxiety and pain associated with pleurodesis. (C)**

Intrapleural administration of sclerosing agents may be painful; significant pain is reported in 7% patients receiving talc to 60% with historical agents such as doxycycline.[57 59] Discomfort can be reduced by administering local anaesthetic via the drain prior to pleurodesis. Lidocaine is the most frequently studied local anaesthetic for intrapleural administration. The onset of action of lidocaine is almost immediate and it should therefore be administered just before the sclerosant. The maximum dose of lidocaine is 3 mg/kg (21 ml of a 1% lidocaine solution for a 70 kg male), with a ceiling of 250 mg. The issue of safety has been highlighted in two studies. Wooten *et al*[60] showed that the mean peak serum concentration of lidocaine following 150 mg of intrapleural lidocaine was 1.3 μg/ml, well below the serum concentration associated with central nervous system side effects (ie, >3 μg/ml). In an earlier study of 20 patients, larger doses of lidocaine were necessary to achieve acceptable levels of local anaesthesia. The patients receiving 250 mg lidocaine had more frequent pain-free episodes than those given 200 mg, while serum levels remained within the therapeutic range. Side effects were limited to transient paraesthesiae in a single patient.[61] The reason for the significant difference in analgesia between the two groups with only a small increment in the lidocaine dose was unclear.

There are no studies to inform a recommendation on the use of premedication and sedation in non-thoracoscopic pleurodesis. Pleurodesis is an uncomfortable procedure and is associated with anxiety for the patient. The use of sedation may be helpful to allay such fears and induce amnesia. The level of sedation should be appropriate to relieve anxiety but sufficient to maintain patient interaction. Sedation employed before pleurodesis should be conducted with continuous monitoring with pulse oximetry and in a setting where resuscitation equipment is available.[62] Further research is underway to address this issue.

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Sclerosant and complications

- **Talc is the most effective sclerosant available for pleurodesis. (A)**
- **Graded talc should always be used in preference to ungraded talc as it reduces the risk of arterial hypoxaemia complicating talc pleurodesis. (B)**
- **Talc pleurodesis is equally effective when administered as a slurry or by insufflation. (B)**
- **Bleomycin is an alternative sclerosant with a modest efficacy rate. (B)**
- **Pleuritic chest pain and fever are the most common side effects of sclerosant administration. (B)**

An ideal sclerosing agent must possess several essential qualities: a high molecular weight and chemical polarity, low regional clearance, rapid systemic clearance, a steep dose-response curve and be well tolerated with minimal or no side effects. The choice of a sclerosing agent will be determined by the efficacy or success rate of the agent, accessibility, safety, ease of administration, number of administrations to achieve a complete response and cost. Despite the evaluation of a wide variety of agents, to date no ideal sclerosing agent exists.

Comparison of sclerosing agents is hampered by the lack of comparative randomised trials, different eligibility criteria and disparate criteria for measuring response and end points. A complete response is usually defined as no reaccumulation of pleural fluid after pleurodesis until death, and a partial response as partial reaccumulation of fluid radiographically but not requiring further pleural intervention such as aspiration. However, some studies use a 30-day cut-off. A recent Cochrane review concluded that thoracoscopic talc pleurodesis is probably the optimal method for pleurodesis.[63] This view is supported by a systematic review.[64] Studies are presently underway investigating other agents including the profibrotic cytokine transforming growth factor β.

Tetracycline

Until recently, tetracycline had been the most popular and widely used sclerosing agent in the UK. Unfortunately, parenteral tetracycline is no longer available for this indication in many countries as its production has ceased.[65]

Sterile talc

Talc ($Mg_3Si_4O_{10}(OH)_2$) is a trilayered magnesium silicate sheet that is inert and was first used as a sclerosing agent in 1935.[66] Talc used for intrapleural administration is asbestos-free and sterilised effectively by dry heat exposure, ethylene oxide and gamma radiation. It may be administered in two ways: at thoracoscopy using an atomiser termed 'talc poudrage' or via an intercostal tube in the form of a suspension termed 'talc slurry'.

Success rates (complete and partial response) for talc slurry range from 81% to 100%.[30 54 56 67–70] The majority of studies have used talc slurry alone and only a limited number of comparative studies have been published (see evidence table available on the BTS website at www.brit-thoracic.org.uk). A truncated randomised study by Lynch and colleagues[71] compared talc slurry (5 g) with bleomycin (60 000 units) and tetracycline (750 mg). Although the study was terminated early because of the removal of tetracycline from the US market, analysis of the data to that point revealed no differences between the three treatment groups 1 month after pleurodesis. In a randomised trial between talc slurry (5 g) and bleomycin (60 000 units), 90% of the talc group achieved a complete response at 2 weeks compared with 79% of the bleomycin group, which was statistically insignificant.[72] Three studies have directly compared talc slurry with talc poudrage (see evidence table available on the BTS website at www.brit-thoracic.org.uk).[73–75] For one randomised study the data are available only in abstract form.[73] It suggests superiority of poudrage over slurry, but limited data are available to validate this conclusion. Of the other two studies, Stefani *et al* compared medical thoracoscopy and talc poudrage with talc slurry in a non-randomised way.[75] Their results suggest superiority of poudrage over slurry, but the two groups were not equal with respect to performance status. In the largest study, Dresler *et al* compared a surgical approach to talc poudrage with talc slurry.[74] They concluded equivalence, but 44% of patients dropped out of the study before the 30-day end point due to deaths and a requirement of 90% lung re-expansion radiologically after intervention to be included in the analysis.

Three studies have compared talc poudrage with other agents administered via an intercostal tube. One compared bleomycin (see below) and the other two tetracyclines (see evidence table available on the BTS website at www.brit-thoracic.org.uk).[76–78] Diacon *et al* concluded that talc insufflation at medical thoracoscopy was superior to bleomycin instillation on efficacy and cost grounds.[76] Kuzdzal *et al* and Fentiman *et al* both showed an advantage of talc insufflation over tetracyclines.[77 78] Each of the three studies analysed fewer than 40 patients.

Talc slurry is usually well tolerated and pleuritic chest pain and mild fever are the most common side effects observed. A serious complication associated with the use of talc is adult respiratory distress syndrome or acute pneumonitis leading to acute respiratory failure. There have been many reports of pneumonitis associated with talc pleurodesis, although predominantly from the UK and the USA where historically non-graded talc has been used.[56 79–87] The mechanism of acute talc pneumonitis is unclear and has been reported with both talc poudrage and slurry.[56 80] This complication is related to the grade of talc used. Maskell and colleagues undertook two studies to determine this association. In the first study they randomised 20 patients to pleurodesis using either mixed talc or tetracycline and compared DTPA clearance in the contralateral lung with that undergoing pleurodesis at 48 h after pleurodesis.[88] DTPA clearance half time decreased by more in the talc group, which is a marker of increased lung inflammation. There was also a greater arterial desaturation in those patients exposed to talc. In the second part of the study, graded (particle size >15 μm) and non-graded (50% particle size <15 μm) talc were compared. There was a greater alveolar–arterial oxygen gradient in the group exposed to non-graded talc at 48 h after pleurodesis. In a subsequent cohort study of 558 patients who underwent thoracoscopic pleurodesis using graded talc, there were no episodes of pneumonitis.[89]

Two studies have investigated the systemic distribution of talc particles in rats after talc pleurodesis. The earlier study using uncalibrated talc found widespread organ deposition of talc particles in the lungs, heart, brain, spleen and kidneys at 48 h. The later study used calibrated talc and found liver and spleen deposition (but no lung deposition) at 72 h, but no evidence of pleurodesis in the treated lungs.[90 91] A further study in rabbits found greater systemic distribution of talc with 'normal' (small particle talc).[92] This supports the evidence from clinical studies that large particle talc is preferable to small particle talc.

Bleomycin

Bleomycin is the most widely used antineoplastic agent for the management of malignant pleural effusions. Its mechanism of action is predominantly as a chemical sclerosant similar to talc

and tetracycline. Although 45% of the administered bleomycin is absorbed systemically, it has been shown to cause minimal or no myelosuppression.[93] Bleomycin is an effective sclerosant with success rates after a single administration ranging from 58% to 85% with a mean of 61%. No studies have demonstrated superiority over talc.[42 71 72 94–102] It has an acceptable side effect profile with fever, chest pain and cough the most common adverse effects.[99 102] The recommended dose is 60 000 units mixed in normal saline. Bleomycin has also been used in studies evaluating small-bore intercostal tubes placed under radiological guidance with similar efficacy rates.[46 48 49 103] In the USA, bleomycin is a more expensive sclerosant than talc, but this is not the case in Europe where non-proprietary formulations are available.[42 72 104]

Rotation following pleurodesis

- **Patient rotation is not necessary after intrapleural instillation of sclerosant. (A)**

Rotation of the patient to achieve adequate distribution of the agent over the pleura has been described in many studies. However, rotating the patient is time consuming, inconvenient and uncomfortable. A study using radiolabelled tetracycline showed that tetracycline is dispersed throughout the pleural space within seconds and rotation of the patient did not influence distribution.[105] A subsequent randomised trial using tetracycline, minocycline and doxycycline revealed no significant difference in the success rate of the procedure or duration of fluid drainage between the rotation and non-rotation groups.[106] A similar study using talc showed no difference in distribution of talc after 1 min or 1 h and no difference in the success rate of pleurodesis at 1 month.[107]

Clamping and removal of intercostal tube

- **The intercostal tube should be clamped for 1 h after sclerosant administration. (C)**
- **In the absence of excessive fluid drainage (>250 ml/ day) the intercostal tube should be removed within 24–48 h of sclerosant administration. (C)**

Clamping of the intercostal tube following intrapleural administration of the sclerosant should be brief (1 h) to prevent the sclerosant from immediately draining back out of the pleural space, although there are no studies to prove that this is necessary.[105] Intercostal tube removal has been recommended when fluid drainage is <150 ml/day, but there is little evidence to support this action.[58 68 108 109] In the only randomised study that has addressed the issue, Goodman and Davies randomised patients to 24 h versus 72 h drainage following talc slurry pleurodesis regardless of volume of fluid drainage. They found no difference in pleurodesis success, although they did not reach the recruitment target based upon the power calculation. In the absence of any evidence that protracted drainage is beneficial, and given the discomfort associated with prolonged drainage, we recommend removal of the intercostal tube within 24–48 h after the instillation of the sclerosant, provided the lung remains fully re-expanded and there is satisfactory evacuation of pleural fluid on the chest x-ray.

Pleurodesis failure

The most likely cause of pleurodesis failure is the presence of trapped lung. There is no reliable way to predict pleurodesis failure: a recent systematic review found that an arbitrary cut-off of pH <7.20 did not predict pleurodesis failure.[15] Where pleurodesis fails, there is no evidence available as to the most effective secondary procedure. We recommend that further evacuation of pleural fluid should be attempted with either a repeat pleurodesis or insertion of indwelling pleural catheter, depending upon the presence of trapped lung. Surgical pleurectomy has been described as an alternative option for patients with mesothelioma (see later).

Malignant seeding at intercostal tube or port site

- **Patients with proven or suspected mesothelioma should receive prophylactic radiotherapy to the site of thoracoscopy, surgery or large-bore chest drain insertion, but there is little evidence to support this for pleural aspirations or pleural biopsy. (B)**

Local tumour recurrence or seeding following diagnostic and therapeutic pleural aspiration, pleural biopsy, intercostal tube insertion and thoracoscopy is uncommon in non-mesothelioma malignant effusions.[110–113] However, in mesothelioma up to 40% of patients may develop malignant seeding at the site of pleural procedures. Three randomised studies have addressed the efficacy of procedure site radiotherapy to prevent tract metastasis (see evidence table available on the BTS website at www.brit-thoracic.org.uk).[114–116] Boutin and colleagues[114] found that local metastases were prevented in patients who received radiotherapy (21 Gy in three fractions) to the site of thoracoscopy. All the patients received radiotherapy within 2 weeks of thoracoscopy. The incidence of tract metastases in the control group in this study was 40%. This study was followed by a longitudinal study that supported its conclusions.[117] In two later studies including sites from a wider range of procedures such as needle biopsy and chest drain, the incidence of tract metastases was not significantly different. Bydder and colleagues showed no benefit of a single 10 Gy radiotherapy fraction to the intervention site in preventing recurrence.[116] All the patients received radiotherapy within 15 days of the procedure, but 46% of procedures were fine needle aspirations. O'Rourke and colleagues used the same radiotherapy dose as Boutin but to smaller fields. They found no benefit of radiotherapy, but again included a range of procedures including needle biopsy. The study included 60 patients but only 16 thoracoscopies, 7 in the radiotherapy group and 9 in the best supportive care group. Tract metastases occurred in 4 patients in the best supportive care group (a rate of 44%) and none in the radiotherapy group.[115] This is very similar to the incidence of tract metastasis in the study by Boutin *et al* (40%). The other procedures were pleural biopsies (45%) and chest tubes (25%). A longitudinal study by Agarwal *et al* found the highest rate of pleural tract metastases in association with thoracoscopy (16%), thoracotomy (24%) and chest tube (9%), but a much lower rate in association with pleural aspiration (3.6%) and image-guided biopsy (4.5%).[118] Careful analysis of the available data therefore supports the use of radiotherapy to reduce tract metastasis after significant pleural instrumentation (thoracoscopy, surgery or large-bore chest drain), but not for less invasive procedures such as pleural biopsy or pleural aspiration. A larger study to specifically address this question would be of use.

A cohort of 38 patients described by West *et al* reported an incidence of pleural tract metastasis after radiotherapy of 5%, but in these cases the metastasis occurred at the edge of the radiotherapy field. Of six patients who received radiotherapy after an indwelling pleural catheter, one subsequently developed pleural tract metastasis.[119] There are, at present, insufficient data on which to make a recommendation about the use of radiotherapy in the presence of indwelling pleural catheters.

The role of prophylactic radiotherapy following pleural procedures in non-mesothelioma malignant effusions has not been established and therefore cannot be recommended.

Intrapleural fibrinolytics

- **Intrapleural instillation of fibrinolytic drugs is recommended for the relief of distressing dyspnoea due to multiloculated malignant effusion resistant to simple drainage. (C)**

The use of fibrinolytic agents to ameliorate symptoms related to complex pleural effusions has been described in several studies although there are no randomised controlled trials.

Davies *et al* found that intrapleural streptokinase increased pleural fluid drainage and led to radiographic improvement and amelioration of symptoms in 10 patients with multiloculated or septated malignant effusions. Intrapleural streptokinase was well tolerated and no allergic or haemorrhagic complications were reported.[120] Gilkeson *et al*[121] preferred urokinase in their prospective but non-randomised study. Twenty-two malignant pleural effusions were treated with urokinase resulting in a substantial increase in pleural fluid output in patients both with and without radiographic evidence of loculations. The majority then underwent pleurodesis with doxycycline resulting in a complete response rate of 56%. Similarly, no allergic or haemorrhagic complications were encountered. In the largest series, 48 patients unfit for surgical release of trapped lung after incomplete lung re-expansion following tube drainage were given intrapleural urokinase.[122] Breathlessness was improved in 29 patients, 27 of whom eventually successfully achieved pleurodesis. This study compared cases with historical controls treated solely with saline flushes and in whom breathlessness was not assessed.

None of these studies is large enough to accurately describe the safety profile of fibrinolytic drugs in this setting. Immune-mediated or haemorrhagic complications have rarely been described with the administration of intrapleural fibrinolytics in contrast to systemic administration of these agents.[123 124] A chest physician should be involved in the care of all patients receiving this treatment.

Thoracoscopy

- **In patients with good performance status, thoracoscopy is recommended for diagnosis of suspected malignant pleural effusion and for drainage and pleurodesis of a known malignant pleural effusion. (B)**
- **Thoracoscopic talc poudrage should be considered for the control of recurrent malignant pleural effusion. (B)**
- **Thoracoscopy is a safe procedure with low complication rates. (B)**

Thoracoscopy (under sedation or general anaesthesia) has grown in popularity as a diagnostic and therapeutic tool for malignant effusions. Under sedation, it is now widely used by respiratory physicians in the diagnosis and management of pleural effusions in patients with good performance status.[125–128] Patient selection for thoracoscopy and talc poudrage is important in view of the invasive nature of the procedure and cost.[129] A significant benefit of thoracoscopy is the ability to obtain a diagnosis, drain the effusion and perform a pleurodesis during the same procedure.

The diagnostic yield and accuracy of thoracoscopy for malignant effusions is >90%.[99 125 127 130 131] Talc poudrage performed during thoracoscopy is an effective method for controlling malignant effusions with a pleurodesis success rate of 77–100%.[6 68 97 132–138] Randomised studies have established the superiority of talc poudrage over both bleomycin and tetracyclines (see evidence table available on the BTS website at www.brit-thoracic.org.uk).[73 76–78] One large randomised study comparing talc poudrage with talc slurry failed to establish a difference in efficacy between the two techniques.[74] A further small non-randomised study comparing these two techniques also established equivalence.[133] A large study has established the safety of talc poudrage using large particle talc; no cases of respiratory failure were seen in this cohort of 558 patients.[89] Talc poudrage is known particularly to be effective in the presence of effusions due to carcinoma of the breast.[139]

Thoracoscopy has less to offer in patients with a known malignant pleural effusion and a clearly trapped lung on the chest x-ray. However, under general anaesthesia, reinflation of the lung under thoracoscopic vision will inform whether the lung is indeed trapped and therefore guide the decision to perform talc poudrage or insert a pleural catheter. The procedure can facilitate breaking up of loculations or blood clot in haemorrhagic malignant pleural effusion and can allow the release of adhesions and thereby aid lung re-expansion and apposition of the pleura for talc poudrage.[140 141]

Thoracoscopy is a safe and well-tolerated procedure with a low perioperative mortality rate (<0.5%).[6 126 129 142] The most common major complications are empyema and acute respiratory failure secondary to infection or re-expansion pulmonary oedema, although the latter may be avoided by staged evacuation of pleural fluid and allowing air to replace the fluid.[127 129 143]

Long-term ambulatory indwelling pleural catheter drainage

- **Ambulatory indwelling pleural catheters are effective in controlling recurrent and symptomatic malignant effusions in selected patents. (B)**

Insertion of a tunnelled pleural catheter is an alternative method for controlling recurrent and symptomatic malignant effusions including patients with trapped lung. Several catheters have been developed for this purpose and the published studies employing them have reported encouraging results.[140 144–147] The presence of foreign material (silastic catheter) within the pleural space stimulates an inflammatory reaction, and vacuum drainage bottles connected to the catheter every few days encourage re-expansion and obliteration of the pleural space. Most catheters can be removed after a relatively short period.

In the only randomised and controlled study to date, Putnam and colleagues[145] compared a long-term indwelling pleural catheter with doxycycline pleurodesis via a standard intercostal tube. The length of hospitalisation for the indwelling catheter group was significantly shorter (1 day) than that of the doxycycline pleurodesis group (6 days). Spontaneous pleurodesis was achieved in 42 of the 91 patients in the indwelling catheter group. A late failure rate (defined as reaccumulation of pleural fluid after initial successful control) of 13% was reported compared with 21% for the doxycycline pleurodesis group. There was a modest improvement in the quality of life and dyspnoea scores in both groups. The complication rate was higher (14%) in the indwelling catheter group and included local cellulitis (most common) and, rarely, tumour seeding of the catheter tract.

The largest series to date reported on 250 patients, with at least partial symptom control achieved in 88.8%. Spontaneous pleurodesis occurred in 42.9% while catheters remained until death in 45.8%.[148] A more recent series of 231 patients treated with an indwelling catheter to drain pleural effusion reported a removal rate of 58% after spontaneous cessation of drainage, with only 3.8% reaccumulation and 2.2% infection.[147] This group included those with trapped lung (12.5% of all patients) or who had failed other therapy. A further series of 48 patients reported a spontaneous pleurodesis rate of 48%.[149] Pien *et al* studied a group of 11 patients in whom an indwelling catheter

was placed specifically for a malignant effusion in the presence of trapped lung; 10 patients reported symptomatic improvement.[144]

A recent series of 45 patients reported by Janes *et al* described three cases of catheter tract metastasis associated with indwelling pleural catheters occurring between 3 weeks and 9 months after insertion. Metastases occurred in 2 of 15 patients with mesothelioma but in only 1 of 30 patients with other metastatic malignancy.[150]

An indwelling pleural catheter is therefore an effective option for controlling recurrent malignant effusions when length of hospitalisation is to be kept to a minimum (reduced life expectancy) or where patients are known or are suspected to have trapped lung and where expertise and facilities exist for outpatient management of these catheters. Although there is a significant cost associated with the disposable vacuum drainage bottles that connect to indwelling pleural catheters, there may be a cost reduction associated with reduced length of hospital stay or avoidance of hospital admission.

Pleurectomy

Pleurectomy has been described as a treatment for malignant pleural effusions. Open pleurectomy is an invasive procedure with significant morbidity. Complications may include empyema, haemorrhage and cardiorespiratory failure (operative mortality rates of 10–19% have been described).[151–153] Pleurectomy performed by video-assisted thoracic surgery has been described in a small series of patients with mesothelioma. There is not sufficient evidence to recommend this as an alternative to pleurodesis or indwelling pleural catheter in recurrent effusions or trapped lung.[154]

Competing interests No member of the Guideline Group is aware of any competing interests.

Provenance and peer review The draft guideline was available for online public consultation (July/August 2009) and presented to the BTS Winter Meeting (December 2009). Feedback was invited from a range of stakeholder institutions (see Introduction). The draft guideline was reviewed by the BTS Standards of Care Committee (September 2009).

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Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010

Helen E Davies,[1,2] Robert J O Davies,[1] Christopher W H Davies,[2] on behalf of the BTS Pleural Disease Guideline Group

[1]Oxford Centre for Respiratory Medicine, Churchill Hospital Site, Oxford Radcliffe Hospital, Oxford, UK
[2]Department of Respiratory Medicine, Royal Berkshire Hospital, Reading, UK

Correspondence to
Dr Christopher Davies, Department of Respiratory Medicine, Royal Berkshire Hospital, Reading RG1 5AN, UK; chris.davies@royalberkshire.nhs.uk

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INTRODUCTION

Pleural infection is a frequent clinical problem with an approximate annual incidence of up to 80 000 cases in the UK and USA combined. The associated mortality and morbidity is high; in the UK 20% of patients with empyema die and approximately 20% require surgery to recover within 12 months of their infection.[1 2] Prompt evaluation and therapeutic intervention appears to reduce morbidity and mortality as well as healthcare costs.[3]

This article presents the results of a peer-reviewed systematic literature review combined with expert opinion of the preferred management of pleural infection in adults for clinicians in the UK. The clinical guidelines generated from this process are presented in figure 1. The guidelines are aimed predominantly at physicians involved in adult general and respiratory medicine and specifically do not cover in detail the complex areas of tuberculous empyema, paediatric empyema or the surgical management of post-pneumonectomy space infection.

HISTORICAL PERSPECTIVE, PATHOPHYSIOLOGY AND BACTERIOLOGY OF PLEURAL INFECTION

This section provides background information for reference, interest and to set the management guidelines in context.

Historical perspective

The Egyptian physician Imhotep initially described pleural infection around 3000 BC, although Hippocrates has been more famously credited with its recognition in 500 BC. Until the 19th century open thoracic drainage was the recommended treatment for this disorder but carried an associated mortality of up to 70%.[4 5] This high mortality was probably due to respiratory failure produced by the large open pneumothorax left by drainage.[5] This was particularly true of *Streptococcus pyogenes* infections which produce streptokinase and large alocular effusions free of adhesions.[5] Closed tube drainage was first described in 1876 but was not widely adopted until the influenza epidemic of 1917–19. An Empyema Commission subsequently produced recommendations that remain the basis for treatment today. They advocated adequate pus drainage with a closed chest tube, avoidance of early open drainage, obliteration of the pleural space and proper nutritional support. These changes reduced mortality to 4.3% during the later stages of this epidemic.

The introduction of antibiotics both reduced the incidence of empyema and changed its bacteriology. Before antibiotics, 60–70% of cases were due to *Streptococcus pneumoniae* which now only accounts for approximately 10% of culture-positive cases.[6] The prevalence of *Staphylococcus aureus* rose and the development of staphylococcal resistance in the 1950s increased complications and mortality.[7 8] More recently, the reported prevalence of anaerobic infections[7 9 10] and Gram-negative organisms[9 10] has risen. Use of intrapleural fibrinolytic therapy was first suggested in 1949[11] but the impure agents available caused adverse reactions. Most recently, early use of video-assisted thoracoscopic surgical (VATS) techniques has been introduced.[12]

Epidemiology of pleural infection

The overall incidence of pleural infection is increasing.[3 13] It is well recognised that pleural infection occurs most commonly in the paediatric and elderly populations and recent large-scale cohort studies concur with this finding. Farjah *et al*[13] studied 4424 patients with pleural infection and observed an increase in incidence of 2.8% per year (95% CI 2.2% to 3.4%). Similarly, in a study population of 11 294, between 1995 and 2003 Finley *et al*[3] found an increase in the pleural infection incidence rate ratio (IRR) of 2.2 (95% CI 1.56 to 3.10) in patients aged <19 years and 1.23 (1.14–1.34) in those aged >19 years. Age-adjusted incidence rates also increased in their cohort by almost 13% during the 8-year period.[3]

Risk factors for pleural infection mirror those for pneumonia although independent considerations for developing empyema include diabetes mellitus, immunosuppression including corticosteroid use, gastro-oesophageal reflux, alcohol misuse and intravenous drug abuse.[2] A history of aspiration or poor oral hygiene is often elicited in anaerobic infection. Iatrogenic pleural infection following pleural interventions and thoracic or oesophageal surgery, trauma or oesophageal perforation account for the majority of remaining cases. Many patients have no apparent risk factors.

Normal pleural fluid physiology

In health, the volume of pleural fluid in humans is small (<1 ml), forming a film about 10 μm thick between the visceral and parietal pleural surfaces.[14] Pleural fluid contains protein at concentrations similar to the interstitial fluid, a small number of cells (predominantly mesothelial cells, macrophages and lymphocytes) and some large molecular weight proteins such as lactate dehydrogenase (LDH). Compared with serum, pleural fluid in health also contains greater levels of bicarbonate, lower levels of sodium and similar

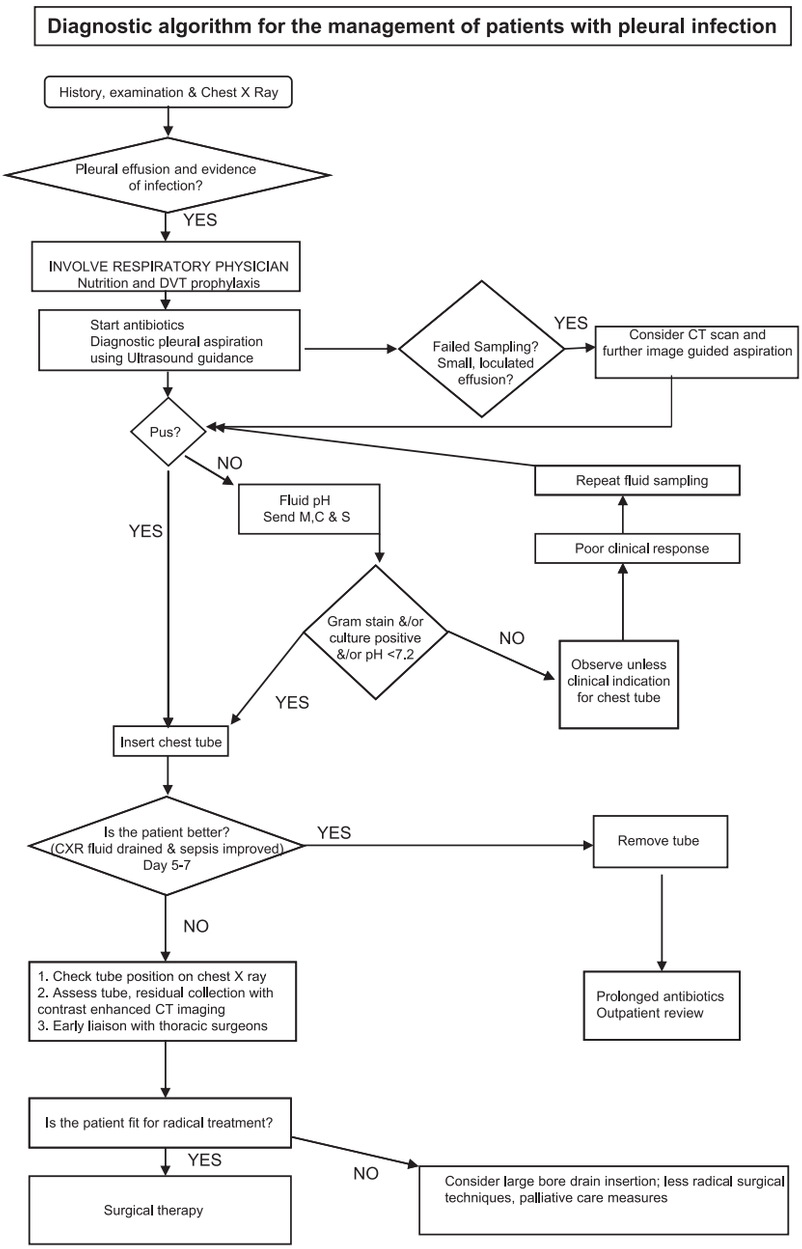

Figure 1 Flow diagram describing the management of pleural infection.

levels of glucose.[15] The pH of normal pleural fluid is around 7.6. These parameters change when disease processes affecting the adjacent lung or vascular tissue activate an immune response.

Water and small molecules pass freely between mesothelial cells, while larger particles may be transported by cytoplasmic transport mechanisms or via pleurolymphatic communications. The pleurolymphatic communication is poorly understood, but probably consists of a series of stomata which connect selected areas of the parietal, mediastinal and diaphragmatic pleura, overlying connective tissues and a series of dilated lymphatic channels.[14]

Pathophysiology of pleural infection

Pneumonia leads to about 110 000 emergency hospital admissions each year in the UK,[16] and the standardised incidence of hospitalisation is increasing (1.98 per 1000 in 2004–5).[16] Up to 57% of patients with pneumonia may develop a pleural effusion[17 18] but, if appropriate antimicrobial therapy is instigated early, the fluid usually resolves. Most forms of pleural infection represent a progressive process that transforms a 'simple' self-resolving parapneumonic pleural effusion into a 'complicated' multiloculated fibrinopurulent collection associated with clinical and/or biochemical features of sepsis. This may significantly impair respiratory reserve and necessitate surgical drainage. Empyema is the presence of pus within the pleural space.

The development of empyema in association with pneumonia is a progressive process and has been classified into three stages as: (1) a simple exudate, (2) a fibrinopurulent stage and (3) a later organising stage with scar tissue (pleural peel) formation.[19]

In the early exudative stage there is fluid movement into the pleural space due to increased capillary vascular permeability. This is accompanied by the production of proinflammatory cytokines such as interleukin 8 (IL-8) and tumour necrosis factor α (TNFα).[20 21] These produce active changes in the pleural

mesothelial cells to facilitate fluid entry into the pleural cavity. Initially, the fluid is a free-flowing exudate characterised by a low white cell count, an LDH level less than half that in the serum, normal pH and glucose levels and does not contain bacterial organisms.[17 22–26] This stage, when the pleural fluid is a straightforward sterile exudate, is often called a 'simple parapneumonic effusion'. Treatment with antibiotics at this stage is likely to be adequate and most effusions of this type do not require chest tube drainage.[17 23 24]

If appropriate treatment is not commenced, a simple parapneumonic effusion may progress to the fibrinopurulent stage with increasing fluid accumulation and bacterial invasion across the damaged endothelium. Bacterial invasion accelerates the immune response, promoting further migration of neutrophils and activation of the coagulation cascade leading to increased procoagulant and depressed fibrinolytic activity.[20 21 27] Increased levels of plasminogen activator inhibitors and decreased tissue-type plasminogen activator (tPA) are seen which favour fibrin deposition and promote formation of septations within the fluid.[20] Neutrophil phagocytosis and bacterial death fuel the inflammatory process by the release of more bacteria cell wall-derived fragments and proteases.[21] This combination of events leads to increased lactic acid and carbon dioxide production resulting in a fall in pleural fluid pH,[28] accompanied by increased glucose metabolism and a rise in LDH levels due to leucocyte death. This leads to the characteristic biochemical features of a fibrinopurulent but not overtly purulent collection that is pH <7.20, glucose <2.2 mmol/l and LDH >1000 IU/l consistent with a 'complicated parapneumonic effusion'.[17] Frank pus is termed 'empyema'.

The final stage is the organising phase in which fibroblasts proliferate.[21] A solid fibrous pleural peel begins to form which occasionally encases the lung preventing re-expansion, impairing lung function and creating a persistent pleural space with continuing potential for infection.

Pleural infection may also develop without evidence of pneumonia—so-called 'primary empyema'.

Bacteriology of pleural infection

The microbiological features of pleural infection have altered significantly in modern times, particularly since the introduction of antibiotic therapies in the 1940s.

Pathogens isolated differ between patients with community or hospital-acquired pleural infection (table 1) and iatrogenic aetiology, for example, following thoracic surgery. Acknowledgement of the differing bacteriology should help to guide empirical antibiotic therapy.

Community-acquired pleural infection

In a recent large trial of 434 patients from over 40 centres in the UK with pleural infection, Gram-positive aerobic organisms were the most frequent organisms identified in community-acquired pleural infection.[2] Streptococcal species including the *S milleri* group of organisms and *S aureus* account for approximately 65% of cases.[2 9 29–44] Gram-negative organisms—for example, Enterobacteriaceae, *Escherichia coli* and *Haemophilus influenzae*—are less commonly cultured and are seen more often in patients with comorbidity.[45]

The frequency of anaerobic isolates is rising and positive pleural fluid cultures in most series report anaerobes in 12–34%.[1 9 29 33 35–38 40 42] However, when identified using different methods such as DNA amplification, anaerobes may be present in up to 76% of cases[7 31 32 46] and may be the only pathogen in about 14% of culture-positive cases.[7 9 29 36 38]

Table 1 Bacteriology of community-acquired and hospital-acquired pleural infection[2]

	Common organisms
Community-acquired	*Streptococcus* spp. (~52%)
	► *S milleri*
	► *S pneumoniae*
	► *S intermedius*
	Staphylococcus aureus (11%)
	Gram-negative aerobes (9%)
	► Enterobacteriaceae
	► *Escherichia coli*
	Anaerobes (20%)
	► *Fusobacterium* spp.
	► *Bacteroides* spp.
	► *Peptostreptococcus* spp.
	► Mixed
Hospital-acquired	Staphylococci
	► Meticillin-resistant *S aureus* (MRSA) (25%)
	► *S aureus* (10%)
	Gram-negative aerobes (17%)
	► *E coli*
	► *Pseudomonas aeruginosa*
	► *Klebsiella* spp.
	Anaerobes (8%)

Infections with anaerobes are more likely to have an insidious clinical onset,[31] with less fever, greater weight loss and are more common following possible aspiration pneumonia and with poor dental hygiene.[31]

Hospital-acquired pleural infection

In patients with hospital-acquired infection, up to 50% of patients with positive pleural fluid cultures isolate *S aureus*.[2] Meticillin-resistant *S aureus* (MRSA) may account for up to two-thirds of cases,[2] although the prevalence of these infections may reduce as greater measures to reduce MRSA infection have been introduced in the last few years. Gram-negative organisms, most commonly *E coli*, *Enterobacter* spp. and *Pseudomonas* spp., are responsible for the majority of the remainder and significantly higher rates of Gram-negative aerobes have been reported in patients who need admission to the intensive care unit.[47 48]

Polymicrobial infection is common with Gram-negative organisms and anaerobes which rarely occur in isolation and which is more frequent in elderly patients and those with comorbid disease.[47 49]

Fungal empyema is rare (<1% of pleural infection).[50] *Candida* species are responsible for the majority[51] and are seen in immunosuppressed individuals. Mortality rates are high (up to 73%).[51]

The microbiological profile of pleural infection also differs between countries and recognition of this, together with awareness of local antibiotic resistance patterns, is required to optimise treatment. In endemic areas such as Thailand pleural infection is reported in up to 22% of patients with pulmonary melioidosis (caused by the Gram-negative bacterium *Burkholderia pseudomallei*).[52] In cases of pleuropulmonary amoebiasis (*Entamoeba histolytica*), pleural infection may arise following rupture of a liver collection and transdiaphragmatic spread.[53]

Despite a clinical picture of pleural infection with biochemical confirmation, pleural fluid culture is negative in approximately 40% of aspirates[2 54] and, although use of PCR may identify causative organisms more sensitively than conventional culturing methods, PCR is not yet a part of routine clinical practice in most UK centres.[2 55]

LITERATURE EVIDENCE AND EXPERT OPINION BEHIND THE GUIDELINE

Respiratory specialist care

- **A chest physician or thoracic surgeon should be involved in the care of all patients requiring chest tube drainage for pleural infection. (C)**

In view of the substantial mortality associated with pleural infection, the small number of cases seen annually in a single centre and the need for prompt effective therapy, focusing the care of patients in specialist hands is appropriate. Delay to pleural drainage is probably associated with increased morbidity, duration of hospital stay,[30 33 36 56–59] and may lead to increased mortality.[30] Misdiagnosis, inappropriate antibiotics and chest tube malpositioning have been cited as important factors contributing to the inadequate management of pleural infection.[56]

An appropriately experienced physician requires the skills to identify patients for surgery and assess thoracic surgical risk, as well as expertise in managing the substantial comorbidities often present. A chest physician best combines these skills as well as having the advantage of an established liaison with thoracic surgical colleagues. In centres with thoracic surgery immediately available, care may be under a physician with a surgical opinion appropriate at any stage in a patient not settling with drainage and antibiotics.

Nutrition

- **Clinicians should ensure adequate nutrition in patients with pleural infection. (C)**

Poor nutrition was identified during the First World War as an adverse determinant of outcome from pleural empyema but is frequently overlooked. Patients with pleural infection suffer catabolic consequences which may lead to further immunodeficiency and slow recovery. Hypoalbuminaemia is associated with a poor outcome from pleural infection[1] and clinicians should provide adequate nutritional support and consider supplemental enteral feeding (ie, nasogastric feeding) from the time of diagnosis.

Thrombosis prophylaxis in pleural infection

- **All patients with pleural infection are at high risk for the development of venous thromboembolism and should receive adequate thrombosis prophylaxis with heparin unless contraindicated. (A)**

All acutely ill patients with pneumonia and/or pleural infection who have been admitted to hospital should receive prophylactic dose low molecular weight heparin treatment unless contraindicated (eg, bleeding, thrombocytopenia, significant renal impairment, allergy to low molecular weight heparins).[60–65] In patients with renal impairment, unfractionated heparin should be used (5000 units subcutaneously twice daily). Mechanical prophylaxis and thromboembolic deterrent stockings should be used in those with contraindications to anticoagulant treatment.

Identification: clinical

- **Features of ongoing sepsis and raised C reactive protein in patients with pneumonia after ≥3 days may indicate progression to pleural infection. (C)**
- **All patients with suspected pleural infection should have blood cultures for aerobic and anaerobic bacteria performed. (C)**

For patients in hospital with community-acquired pneumonia the median time to improvement in heart rate and blood pressure is 2 days, and 3 days for temperature, respiratory rate and oxygen saturation.[66] A failure to respond to initial management may indicate the presence of a parapneumonic effusion or empyema as a complication of pneumonia.

Indicators of possible progression of pneumonia to pleural infection include ongoing fever and symptoms or signs of sepsis—for example, elevated white cell count and/or inflammatory markers such as C reactive protein (CRP). CRP is a sensitive marker of progress in pneumonia.[67 68] Failure of the CRP level to fall by 50% is associated with an adverse outcome and increased incidence of empyema[69] and should prompt further evaluation including a repeat chest x-ray.

A recent study[70] used a number of pneumonia severity scores and clinical variables to predict the likelihood of development of complicated parapneumonic effusion and empyema in patients with community-acquired pneumonia. None of the severity scores had any predictive value but seven clinical variables were identified predicting development of pleural infection. The presence of chronic obstructive pulmonary disease was associated with reduced risk of progression to pleural infection, but the following variables were positively predictive: (1) albumin <30 g/l; (2) CRP >100 mg/l; (3) platelet count $>400\times10^9$/l; (4) sodium <130 mmol/l; (5) intravenous drug abuse; and (6) chronic alcohol abuse. Using two or more points as the cut-off, the sensitivity was 87%, specificity 68.3%, positive predictive value 17.7% and negative predictive value 98.5%. The scoring system requires independent prospective validation.

Blood cultures for bacteria are positive in about 14% of patients with pleural infection[2] and, when positive, are often the only source of positive microbiology. Blood cultures should therefore be performed in all patients with suspected pleural infection.

Identification: imaging

Initial imaging

Empyema should be suspected in all patients who fail to respond to appropriate antibiotic therapy. A pleural effusion may be obvious on the chest x-ray[71] and the coexistence of pulmonary infiltrates and fluid should alert the clinician to the possibility of a parapneumonic collection. Lateral chest x-rays may confirm pleural fluid not suspected on the posteroanterior chest x-ray,[17] however pleural ultrasonography is widely available and is the preferred investigation. Ultrasound enables determination of the exact location of any fluid collection and guided diagnostic aspiration can be performed if required.[71 72] Increasingly, thoracic ultrasound is being performed alongside the chest x-ray in patients with suspected pleural infection. However, unlike chest radiography, ultrasound is not yet routinely available in outpatient settings and out of hours so, for monitoring/follow-up purposes, the chest x-ray remains the initial imaging investigation of choice.

Pleural sepsis is occasionally caused by oesophageal rupture and this diagnosis should be suspected in patients who develop a pleural effusion soon after significant retching or vomiting. Diagnostic strategies to identify this important problem are oesophageal imaging (eg, a contrast-enhanced swallow assessment) and measurement of pleural fluid amylase levels which are raised as swallowed salivary amylase enters the pleural space through the oesophageal perforation.[73 74] The detection of an oesophageal leak should prompt immediate referral to a surgeon with expertise in the management of oesophageal rupture.

Further radiological assessment

Ultrasound

Pleural ultrasonography may help to identify pleural infection. In a study of 320 cases of pleural effusion,[75] all echogenic

effusions were caused by exudates and homogeneous echogenic effusions were due to either empyema or haemorrhage.

Correlation between the presence of loculated pleural fluid and a significantly lower pleural fluid pH and glucose and a high LDH concentration has been shown,[76 77] although this has not been corroborated by further studies.

CT scanning

Contrast-enhanced CT scanning with the scan performed in the tissue phase may be of value in patients when the diagnosis is in doubt or an underlying abnormality is thought either to be associated with the empyema or potentially its cause, such as an oesophageal perforation or bronchogenic carcinoma. CT scanning can help to differentiate pleural empyema from a parenchymal lung abscess and may also help to formulate management decisions about drainage, providing guidance for drain insertion and determination of subsequent tube positioning and success of drainage attempts, and the need for surgical intervention.

Empyemas are usually lenticular in shape and compress the lung parenchyma, while lung abscesses often have an indistinct boundary between the lung parenchyma and collection.[78 79] The 'split pleura' sign caused by enhancement of both parietal and visceral pleural surfaces (figure 2) and their separation in empyema is characteristic of a pleural collection. Pleural thickening is seen in 86–100% of empyemas[80–82] and 56% of exudative parapneumonic effusions.[80] Pleural thickness on contrast enhanced CT scans is greater in those with frankly purulent effusions,[83] whereas the absence of pleural thickening suggests a simple parapneumonic collection.[80] Where pleural infection has progressed, pleural enhancement may be demonstrated with contrast-enhanced CT scanning[82] and increased attenuation of extrapleural subcostal fat is often seen.[78 80–82] These signs are absent in transudative effusions.[81] Moderate (<2 cm) mediastinal lymphadenopathy is seen in over one-third of patients with pleural infection.[83]

MRI

MRI is not routinely indicated and offers no advantage over CT scanning for pleural infection; however, it may be considered in specific situations such as allergy to contrast agents or young/pregnant patients where minimising ionising radiation exposure is a particular priority. MRI can also help to define chest wall involvement with the infection (eg, empyema necessitans or tuberculous empyema).

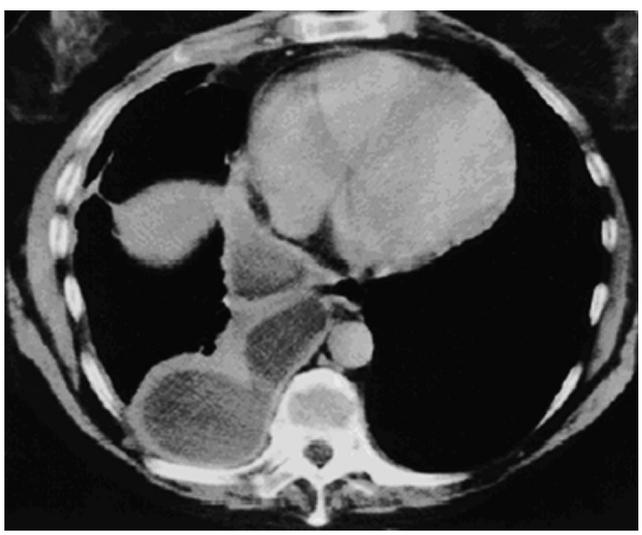

Figure 2 Typical contrast-enhanced CT appearances of pleural empyema. The image shows a multiloculated pleural collection forming separate lenticular pleural opacities. The 'split pleura' sign with enhancing pleural tissue visible on both the visceral and parietal pleural surfaces is shown.

Identification: pleural fluid aspiration

- **All patients with a pleural effusion in association with sepsis or a pneumonic illness require diagnostic pleural fluid sampling. (C)**

If a pleural effusion is identified on the chest x-ray of a patient with possible pleural infection, it is impossible clinically to differentiate the presence of a complicated parapneumonic effusion requiring chest tube drainage from a simple effusion that may resolve with antibiotics alone. There are also no specific data relating to which patients with a parapneumonic effusion can be managed without diagnostic pleural fluid sampling. Sometimes patients seen initially in the community by their general practitioner will have spontaneous resolution of parapneumonic effusions in conjunction with antibiotics without any pleural sampling by the time they present to respiratory specialists. This cohort often present following referral to the outpatient setting with an undiagnosed pleural effusion and repeat imaging confirms radiological improvement.

Although empyemas are more common in men than in women,[1 9 33 57 84] there are no differences in patient age, white cell count, peak temperature, presence of chest pain and extent of radiological infiltrate between patients requiring chest tube drainage for symptom resolution and those who resolve with antibiotics alone.[17]

Pleural fluid characteristics remain the most reliable diagnostic test to guide management,[17 22–24 77 85–87] and diagnostic pleural fluid sampling is therefore recommended in all patients with a pleural effusion >10 mm depth in association with a pneumonic illness or recent chest trauma or surgery and who have features of ongoing sepsis.

Imaging guidance should be used since this minimises risks of organ perforation[88] and improves the recovery rate of pleural fluid.[89] Sampling using thoracic ultrasound is simple, safer and will reduce patient discomfort (see guideline on pleural investigation).[71 89 90] Sampling can be performed by sterile procedure using a needle and syringe with local anaesthetic if necessary.

Small effusions (ie, <10 mm thickness) will usually resolve with antibiotics alone.[17 25] Observation may be appropriate for these patients, but an increase in the size of the effusion or ongoing sepsis should warrant re-evaluation and diagnostic pleural fluid sampling.

Patients in an intensive care unit frequently develop pleural effusions that are not caused by pleural infection.[91] It is probably safe to observe such patients with hypoalbuminaemia, heart failure or atelectasis who are at low risk of infection while treating the underlying condition.[91] Pleural fluid should be sampled if there are features of sepsis using ultrasound guidance, particularly in patients receiving positive pressure ventilation.

- **Pleural fluid pH should be assessed in all non-purulent effusions when pleural infection is suspected. (B)**
- **If pleural fluid pH measurement is not available, pleural fluid glucose assessment should be performed where pleural infection is possible. (B)**

The presence of frank pus is diagnostic of an empyema and therefore, following aspiration, the appearance of the pleural fluid should be recorded. The pH of the pleural fluid of all non-purulent aspirates should be measured immediately. Protein

concentration and microbiological culture analysis should be routinely requested on all initial samples. Pleural fluid cytology and acid/alcohol fast bacilli analysis for mycobacteria should be performed if clinically indicated. Further details are given in the BTS pleural investigation guideline.

Pleural fluid from parapneumonic effusions or empyema is an inflammatory exudate and absolute pleural fluid protein values are of no value in determining the likelihood of spontaneous resolution of the effusion or chest tube drainage requirements.[17 23 24 87] Polymorphonuclear (PMN) leucocytes dominate, but the total pleural fluid leucocyte count varies widely between simple effusions and empyemas.[24] A predominance of lymphocytes in an exudate should raise the possibility of malignancy or tuberculosis.

Pleural fluid for pH analysis should be collected anaerobically (as the presence of air can falsely elevate pleural fluid pH values[92]) in a heparinised blood gas syringe and then measured in a blood gas analyser. Physicians should be aware that lidocaine is acidic and can depress measured pH,[92] so a different syringe (devoid of residual lidocaine after local anaesthetic administration) should be used for pleural fluid sampling.[92 93] It is not advisable and should not be necessary to put frank pus through a blood gas analyser as this already indicates a need for chest tube drainage of the effusion. However, where there is uncertainty about whether a turbid/cloudy fluid is infected, pH can be measured safely using a blood gas analyser. Extensive clinical experience of this technique, particularly in the USA, has shown it does not damage the blood gas analyser. Measurement of pleural fluid pH is unreliable when analysed by pH litmus paper or a pH meter, and these should not be considered an acceptable alternative to a blood gas analyser.[94 95]

A patient with pleural infection requiring drainage will develop a pleural fluid acidosis associated with a rising LDH level and a falling glucose level.[17 24 85] Data from a systemic meta-analysis reviewing these criteria have justified their use.[85] This report showed that a pleural fluid pH of <7.2 is also the single most powerful indicator to predict a need for chest tube drainage, and that pleural fluid LDH (>1000 IU/l) and glucose (<3.4 mmol/l) did not improve diagnostic accuracy. Where pleural fluid pH measurement is not available glucose and LDH should be measured, a pleural fluid glucose level <3.4 mmol/l may be used as an alternative marker to indicate a need for chest drain insertion. However, pleural fluid glucose may be lowered in situations other than pleural infection, such as rheumatoid effusions, and this should be borne in mind when interpreting the result.

Studies have shown that non-purulent collections with biochemical evidence of infection are likely to require chest tube drainage for adequate resolution of sepsis.[17 21 22 24 25 28 59 77 85 86]

Occasionally a pleural fluid pH of >7.6 will be obtained in a complicated parapneumonic effusion as a result of infection with *Proteus* spp. Its ability to produce ammonia by urea splitting can produce alkalotic fluid.[96]

If a single pleural fluid sample appears out of context with the clinical status of the patient and the ultrasound appearances, it may be of value to repeat the aspiration. A small series of multiple locule sampling showed that the biochemistry may be different in different locules.[97]

Pleural fluid cytokine and/or inflammatory mediator levels (eg, IL-8, TNFα, vascular endothelial growth factor or CRP) may be useful to differentiate complicated parapneumonic effusions from other exudative collections.[98–101] Further studies are required to elicit their exact role.

Indications for pleural fluid drainage in pleural infection

- **Patients with frankly purulent or turbid/cloudy pleural fluid on sampling should receive prompt pleural space chest tube drainage. (B)**

The presence of frankly purulent or turbid/cloudy fluid on pleural aspiration indicates the need for prompt chest tube drainage.[17 24 85 86] Purulent fluid is more frequent in patients who fail chest tube drainage and require surgery or who die.[57]

- **The presence of organisms identified by Gram stain and/or culture from a non-purulent pleural fluid sample indicates that pleural infection is established and should lead to prompt chest tube drainage. (B)**

The presence of organisms identified by positive Gram stain indicates bacterial invasion and implies progression from a simple effusion into a complicated parapneumonic effusion and hence the need for chest tube drainage.[17 24 85 86] However, some frankly purulent or culture-positive parapneumonic effusions due to *S pneumoniae* may resolve with antibiotics alone, avoiding chest tube drainage.[18 87] Decisions regarding pleural drainage should be made on an individual basis.

- **Pleural fluid pH <7.2 in patients with suspected pleural infection indicates a need for chest tube drainage. (B)**
- **Parapneumonic effusions that do not fulfil any of these criteria for chest tube drainage could be treated with antibiotics alone provided clinical progress is good. (B)**
- **Poor clinical progress during treatment with antibiotics alone should lead to prompt patient review, repeat pleural fluid sampling and probably chest tube drainage. (B)**

Some patients with an initial pleural pH >7.2 will fail to resolve their sepsis syndrome and will need chest tube drainage and even subsequent surgery.[57] These occasional cases confirm that, while pleural pH is adequately specific in predicting the need for pleural drainage, it is less than 100% sensitive[57] and does not accurately predict mortality or eventual need for surgical intervention.[17 57] One reason for this is the heterogeneity of the biochemical characteristics in multiloculated effusions, such that sampling different infected locules can result in markedly different indices of disease severity.[97] Unsatisfactory clinical progress therefore indicates a need for repeated pleural fluid sampling and possible chest tube drainage.

- **Patients with a loculated pleural collection should receive early chest tube drainage. (C)**
- **Large non-purulent effusions could be drained by aspiration and/or chest tube if required for symptomatic benefit. (C)**

When needle aspiration is straightforward, it may occasionally be possible to remove all the fluid at initial pleural fluid aspiration. In some cases the fluid will not re-accumulate and no further intervention will be required.

The presence of loculation on chest radiography or ultrasonography[24 77 102] is associated with a poorer outcome and may be an additional indication for early chest tube drainage. Larger pleural collections (>40% of the hemithorax) may be more likely to require surgery.[1 102]

Chest tube drainage

- **A small-bore catheter 10–14 F will be adequate for most cases of pleural infection. However, there is no consensus on the size of the optimal chest tube for drainage. (C)**
- **If a small-bore flexible catheter is used, regular flushing is recommended to avoid catheter blockage. (C)**

- **Chest tube insertion should be performed under imaging guidance wherever possible. (D)**

Chest tube insertion should be performed in line with the BTS pleural procedures guidelines[103] (***see page ii61***) and recent National Patient Safety Agency recommendations.[88] Image guidance should be used whenever available, particularly as many infected effusions will be loculated.

The clinical outcome of patients with pleural infection treated with differing sized chest drains has not been addressed in a randomised controlled trial and there remains no clinical consensus on the optimal choice, with widely differing opinions between the medical and surgical specialities. Traditionally, closed chest tube drainage of pus from the pleural cavity has been via large-bore (>28 F) chest tubes inserted without radiological guidance. More recently, flexible small-bore catheters (10–14 F) have been employed, which are easier and less traumatic to insert and may be more comfortable for the patient.

In a large randomised trial assessing intrapleural fibrinolytic agents, subanalysis revealed no increased efficacy with large-bore tubes compared with small-bore drains.[84] Previously published data suggest that image-guided small-bore catheters can have a good outcome, both as the initial drainage procedure[104–108] and as a rescue treatment when larger tubes have failed.[104–111] 10–14 F catheters are popular in these series and have a low complication rate.[71 105 107 111 112] There is, however, still a substantial body of opinion, based on anecdotal clinical experience, which considers large-bore tubes to be more effective for draining thick pus. Sound clinical trials are needed to clarify the optimal chest tube size.

No randomised controlled trial data exist evaluating optimal drain management issues such as flushing and drain suction. In most studies assessing small-bore catheters both flushing and suction were used,[71 104 105 107 108 111 113] which may improve drainage efficiency by reducing blockage of the catheter from fibrinous debris. Regular flushing (eg, 20–30 ml saline every 6 h via a three-way tap) is therefore recommended for small catheters, preferably administered by trained nurses. Flushing larger bore drains is technically more difficult as these do not routinely have three-way taps and disconnection for irrigation might encourage introduction of secondary infection.

Application of suction (−20 cm H_2O) is employed in the belief that it improves drainage, but there is no adequate trial evidence or clinical consensus on which to base specific guidelines in this area.[114 115]

For further details on insertion of intercostal chest drains, readers are referred to the BTS pleural procedures guidelines[103] and the section in this document on pleural procedures and thoracic ultrasound.

Antibiotics

- **All patients should receive antibiotics targeted to treat the bacterial profile of modern pleural infection and based on local antibiotic policies and resistance patterns. (B)**
- **Antibiotics to cover anaerobic infection should be used in all patients except those with culture proven pneumococcal infection. (B)**
- **Macrolide antibiotics are not indicated unless there is objective evidence for or a high clinical index of suspicion of 'atypical' pathogens. (B)**
- **Where possible, antibiotic choice should be guided by bacterial culture results and advice from a microbiologist. (B)**
- **Penicillins, penicillins combined with β-lactamase inhibitors, metronidazole and cephalosporins penetrate the pleural space well. Aminoglycosides should be avoided. (B)**
- **When bacterial cultures are negative, antibiotics should cover both common community-acquired bacterial pathogens and anaerobic organisms. (B)**
- **Empirical antibiotic treatment for hospital-acquired empyema should include treatment for MRSA and anaerobic bacteria. (B)**
- **Intravenous antibiotics should be changed to oral therapy once there is clinical and objective evidence of improvement in sepsis. (D)**
- **Intrapleural antibiotics are not recommended. (D)**
- **Prolonged courses of antibiotics may be necessary and can often be administered as an outpatient after discharge. (D)**

As soon as pleural infection is identified, all patients should receive antibiotic therapy and, where possible, this should be chosen based on results of pleural fluid or blood culture and sensitivities. Most patients with pleural infection will have had antibiotics already. However, despite this, in a recent randomised trial 54% of patients with pleural infection had positive pleural fluid cultures and 12% positive blood culture results.[84] Those with positive blood cultures often had no other positive microbiology results, emphasising the importance of taking blood cultures from all patients with suspected pleural infection.[84]

A significant proportion of both aerobes and anaerobic organisms from pleuropulmonary infection may demonstrate resistance to penicillin,[7 116 117] but β-lactams remain the agents of choice for *S pneumoniae*[118] and *S milleri* infections.[119 120] Aminopenicillins, penicillins combined with β-lactamase inhibitors (eg, co-amoxiclav, piperacillin-tazobactam) and cephalosporins show good penetration of the pleural space.[34 121–124] Aminoglycosides should be avoided as they have poor penetration into the pleural space and may be inactive in the presence of pleural fluid acidosis.[34 125–128] There is no evidence that administering antibiotics directly into the pleural space offers any advantage.

In the absence of positive culture results, empirical antibiotics should be chosen to cover likely pathogenic organisms. There are a considerable number of reasonable drug combinations and the chosen regimen should reflect whether the infection was community- or hospital-acquired, local hospital policies and antibiotic resistance patterns.

In community-acquired infection, treatment with an aminopenicillin (eg, amoxicillin) will cover organisms such as *S pneumoniae* and *H influenzae*,[129] but a β-lactamase inhibitor such as co-amoxiclav or metronidazole should also be given because of the frequent co-existence of penicillin-resistant aerobes including *S aureus* and anaerobic bacteria.[7 117 130] A synergistic role of anaerobes with the *S milleri* group of organisms has been postulated.[131 132]

Clindamycin achieves good penetration of the infected pleural space[126 133 134] and offers adequate antimicrobial cover for these patients. Patients with a penicillin allergy can therefore be treated by clindamycin alone[7 129] or in combination with ciprofloxacin or a cephalosporin.[135] Chloramphenicol, carbapenems such as meropenem, third generation cephalosporins and broad-spectrum antipseudomonal penicillins such as piperacillin also have good anti-anaerobic activity and are alternative agents.[116 136]

Pleural effusions may occur in patients with *Legionella* pneumonia but are usually self-resolving.[137] Although *Legionella* was not identified in a large recent series of UK adult pleural

infections,[2] it has rarely been reported as a cause of empyema[138] and a macrolide antibiotic should be added in proven/suspected cases, although use of these antibiotics is not routinely recommended. Similarly, pleural effusions may occur in 5–20% of patients with pneumonia due to *Mycoplasma pneumoniae*.[139 140] These are usually small reactive effusions which will resolve with suitable antibiotics, but diagnostic pleural fluid sampling may be needed to exclude a complicated parapneumonic effusion or empyema. In all cases, antibiotic regimens should be adjusted according to the subsequent culture results (while remembering that anaerobic pathogens are difficult to grow and having a low threshold for anti-anaerobic coverage).

In hospital-acquired empyema, usually secondary to nosocomial pneumonia, trauma or surgery, antibiotics should be chosen to treat both Gram-positive and Gram-negative aerobes and anaerobic organisms (see table 1). Recent studies show that there is a significant increase in MRSA infection causing hospital-acquired pneumonia and empyema, so empirical antibiotics for the latter should initially include cover for MRSA until microbiological results are available.[2 141–144]

Intravenous administration of antibiotics is often appropriate initially but can be changed to the oral route when objective clinical and biochemical improvement is seen. The duration of treatment for pleural infection has not been assessed in detailed clinical trials, however antibiotics are often continued for at least 3 weeks, again based on clinical, biochemical (eg, CRP) and radiological response.

Intrapleural fibrinolytics

- **There is no indication for the routine use of intrapleural fibrinolytics in patients for pleural infection. (A)**

Intrapleural fibrinolytic therapy was first used in 1949.[11] More recently, observational series[11 145–169] and small randomised trials[149 170–178] showed these agents improved pleural fluid drainage, and it was therefore widely assumed they would improve long-term patient outcome. However, a recent large randomised trial showed that these short-term drainage benefits are not associated with reduced mortality, the frequency of surgery, the length of hospital stay or long-term radiological and lung function outcome.[84] This trial used intrapleural streptokinase that was associated with an excess of immunological adverse reactions such as fever, leucocytosis and malaise,[148 156 165 179 180] but no excess of systemic or intrapleural bleeding and no systemic activation of the fibrinolytic cascade,[84] in contrast to previous isolated reports of local pleural haemorrhage,[156 163 168] systemic bleeding[153] and epistaxis[156] associated with its administration.[151] Thus, current evidence does not support the routine use of intrapleural fibrinolytic agents. On occasions, such treatment may be indicated for the physical decompression of multiloculated (and so tube drainage-resistant) pleural fluid collections that are responsible for dyspnoea or respiratory failure if discussion with a thoracic surgeon identifies that either surgery is not immediately possible due to additional patient co-morbidity, the feasibility of transfer to a surgical unit or other clinical or logistical reasons.

Urokinase is non-antigenic but may still cause acute reactions (due to immediate hypersensitivity and histamine release) with fever[150] and cardiac arrhythmia.[181] There is a report of adult respiratory distress syndrome in a patient who received both streptokinase and urokinase for empyema drainage.[182]

Doses of fibrinolytics used in studies have varied but include streptokinase 250 000 IU daily[11 145 147–149 151–157 160 163 165 167 169 170 173–176 179] or 250 000 IU 12-hourly[84 151] or urokinase 100 000 IU daily[170 171 178] retained for 2–4 h in the pleural space.

There is currently interest in other intrapleural agents including combination therapy with fibrinolytics and fluid viscosity and biofilm-disrupting agents such as streptodornase and deoxyribonuclease (DNase).[183 184] In experimental/translational studies, this combination reduced infected pus viscosity when compared with fibrinolytics (streptokinase) alone and can disrupt infected biofilms.[183–187] Such therapeutic combinations are currently in human clinical trials. Preliminary results from one of these trials suggests that a combination of intrapleural tPA and DNase may provide superior drainage to a fibrinolytic alone, but full publication of these results is awaited.

Timing of chest drain removal in pleural infection

Removal of the chest drain is appropriate after radiological confirmation of successful pleural drainage—that is, reduction in the size of the pleural collection on the chest x-ray or thoracic ultrasound—and objective evidence of sepsis resolution—that is, improvement in temperature and clinical condition and decreasing inflammatory markers (eg, CRP). Inpatient observation for 24 h after drain removal is usual, although a longer period of rehabilitation may be necessary as most patients will have been unwell and in hospital for a prolonged period.

Persistent sepsis and pleural collection

- **Patients with persistent sepsis and a residual pleural collection should undergo further radiological imaging. (C)**
- **Patients with persistent sepsis and a residual pleural collection should be discussed with a thoracic surgeon to consider all possible surgical options available. (D)**

In patients who do not respond to antibiotics and chest drainage with ongoing signs of sepsis in association with a persistent pleural collection, the diagnosis should be reviewed and a further chest x-ray and CT scan or thoracic ultrasound performed. Contrast-enhanced thoracic CT scanning more accurately identifies chest tube position, the anatomy of the effusion, presence of pleural thickening and may also identify endobronchial obstruction and mediastinal pathology.[188–193] Pleural thickening may represent development of a fibrinous 'peel' which may prevent lung re-expansion and hence pleural apposition regardless of adequacy of fluid drainage.[188 192 194–196] CT scanning cannot accurately differentiate early from late fibrinopurulent stage disease,[82] and pleural thickness on the CT scan does not appear to predict long-term outcome from tube drainage.[57] A pleural 'peel' may resolve over several weeks and persisting with medical therapy over this period in stable patients may prevent the need for surgery.[196] Residual calcification,[82] thickening of extrapleural tissues[82] and pleural scarring[196] may be seen on imaging long after resolution of an empyema.

Patients with persistent sepsis

- **Patients should receive surgical treatment if they have persisting sepsis in association with a persistent pleural collection, despite chest tube drainage and antibiotics. (C)**
- **Failure of chest tube drainage and antibiotics should prompt early discussion with a thoracic surgeon. (C)**

No objective criteria exist to define the point at which surgical intervention for control of pleural infection is required and the decision to operate on a patient remains subjective. Although previous observational studies have indicated that patients with purulent fluid[57] and/or loculations[102] at presentation are more likely to require surgery, many of these patients will settle without an operation and recent data indicate these features are not predictive.[84 197] Patients should be considered for surgery if they have ongoing signs of sepsis in association with a persistent

pleural collection despite drainage and antibiotics. Failure of sepsis to resolve within 5–7 days[39 198] is suggested as an appropriate period following which a surgical opinion should be sought. Discussion with a thoracic surgeon should be considered in all cases failing to respond.

VATS is increasingly used as first-line therapy although open thoracic drainage or thoracotomy and decortication remain alternative techniques. The type of procedure performed will depend on many factors including patient age and comorbidity, surgeons' preferences and local equipment availability. The choice of surgical procedure is beyond the remit of these guidelines and is not considered further.

Two small unblinded randomised trials have directly compared surgical and medical therapy. Wait *et al*[12] studied 20 patients with pleural infection who were suitable for general anaesthesia and randomised them to receive either immediate VATS or chest tube insertion (by junior resident medical staff) with additional instillation of intrapleural streptokinase for 3 days. The surgical group had higher primary treatment success (10/11 patients) and all streptokinase medical failures (5/9 patients) were salvaged by surgery without requiring thoracotomy.[12] Surgical patients also had a shorter drainage period (5.8 vs 9.8 days) and hospital stay (8.7 vs 12.8 days). The results of this study are of doubtful robustness as the trial was very small, had an unusually high clinical failure rate in the control limb (55%) which explains the positive result, and was not blinded and so open to bias.

Bilgin *et al*[199] randomised 70 patients with pleural infection to immediate VATS under local anaesthesia with sedation (n=29) or general anaesthesia if this was not tolerated (n=6) versus chest tube drainage (n=35). Both groups received antibiotic therapy. In the VATS group, initial treatment success was achieved in 82.8% (ie, no indication for subsequent open thoracotomy and decortication) compared with 62.9% in the tube drainage group. The mean hospital stay was 8.3 days for the VATS group and 12.8 days in the tube drainage arm ($p<0.05$).[199] Interpretation of the results, however, should be carefully considered as the authors did not clearly specify the primary outcome measure and the indications prompting further surgical intervention were highly subjective. Further appropriately powered and blinded trials are needed in this area.

- **The choice of antibiotic should be reviewed and a prolonged course administered where appropriate. (D)**
- **A thoracic surgeon should be involved in assessment of suitability for anaesthesia. Less radical surgical interventions including rib resection and placement of a large-bore drain may be considered in frail patients depending on surgical expertise and access and can be performed in some cases under local anaesthetic or with epidural anaesthesia. (C)**
- **In patients with ineffective effusion drainage and persistent sepsis who are unable to tolerate general anaesthesia, re-imaging of the thorax and placement of a further image-guided small-bore catheter, a larger-bore chest tube or intrapleural fibrinolytic could be considered after discussion with a thoracic surgeon. (D)**
- **For some patients, palliative treatment and active symptom control measures will be appropriate. (D)**

Ineffective chest tube drainage and persistent sepsis in patients unfit for radical treatment can be approached by a number of 'less invasive' options. Re-imaging the thorax and placement of further image-guided small-bore catheters may drain loculated collections[105–109 111] and larger bore chest tubes can be tried for 'thick' pus.[112] Alternatively, patients may proceed to surgical rib resection and open drainage under general or local anaesthesia; continued liaison with a thoracic surgeon should continue in achieving optimal management. The prolonged period (often months) of recovery following this procedure can contribute to increased patient morbidity and this must be discussed with patients during procedural consent.

For some patients with empyema who are unfit for radical treatment, further drainage may not be acceptable and, in these cases, ongoing sepsis and impaired respiratory function can lead to an unrelenting decline and subsequent death. When these patients are identified, palliative symptom control delivered by a multidisciplinary team may be appropriate.

Bronchoscopy

- **Bronchoscopy should only be performed in patients where there is a high index of suspicion of bronchial obstruction. (C)**

The role of bronchoscopy in patients with empyema has not been addressed specifically by any studies. In one series, 43/119 patients (36%) with empyema underwent bronchoscopy and tumour was found in only five patients.[1] Bronchoscopy is usually performed at the time of surgery by most thoracic surgeons but, again, only a small number of these patients have obstructing tumour predisposing to their empyema.[40] Bronchoscopy is therefore only recommended where there is a high index of suspicion for bronchial obstruction—for example, a mass or volume loss on radiographic imaging or a history of possible foreign body which may predispose to the pleural infection itself.

Follow-up

- **All patients with empyema and pleural infection require outpatient follow-up. (D)**

Outpatient follow-up with a repeat chest x-ray and inflammatory markers should be arranged for all patients, often within 4 weeks following discharge, and continued outpatient care may be required for several months depending on progress. Persistent elevation of patients' inflammatory markers should prompt further imaging and be interpreted in combination with their clinical status. Patients should be advised to return for prompt medical attention if recurrent symptoms develop since late relapse of pleural infection is well recognised.

Prognosis in pleural infection

The long-term survival of patients with pleural infection is good if prompt treatment is initiated. In a series of 85 patients followed for up to 4 years, the mortality was 14% and all deaths occurred within the first 400 days after drainage.[57] Deaths were usually due to comorbid conditions and not directly due to sepsis from the empyema.

No reliable clinical, radiological or pleural fluid characteristics accurately determine patients' prognosis at initial presentation. Hypoalbuminaemia, the presence of loculated fluid and anaerobic infections have been related to adverse outcome in previous studies[1 76 77] although not in recent reports.[2 57]

Long-term sequelae of pleural empyema may include residual pleural thickening (up to 13% of patients).[200] This is not usually associated with functional impairment although, rarely, extensive incapacitating pleural fibrosis may develop (fibrothorax).[135 200 201] Surgical decortication may occasionally provide symptomatic benefit for patients with a fibrothorax. Pleural calcification, bronchopleural fistula formation and development of empyema necessitans (disruption of the parietal pleura with spontaneous discharge of pleural contents evident under the chest wall) are other rare complications.

Pyothorax-associated lymphoma

Pleural lymphoma is rare. It may arise in approximately 2% of patients with a long-standing pyothorax (>20 years), usually following induction of an artificial pneumothorax for tuberculosis.[202–211] It predominantly occurs in Japanese populations, with few reports of cases from the Western world.[202 210] Histologically, it is a non-Hodgkin's lymphoma with a distinctive B cell phenotype. The exact pathogenesis remains unclear, however there is a recognised association with Epstein–Barr virus infection.[203 207 208 211 212]

Competing interests No member of the Guideline Group is aware of any competing interests.

Provenance and peer review The draft guideline was available for online public consultation (July/August 2009) and presented to the BTS Winter Meeting (December 2009). Feedback was invited from a range of stakeholder institutions (see Introduction). The draft guideline was reviewed by the BTS Standards of Care Committee (September 2009).

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Local anaesthetic thoracoscopy: British Thoracic Society pleural disease guideline 2010

Najib M Rahman,[1] Nabeel J Ali,[2] Gail Brown,[3] Stephen J Chapman,[1] Robert J O Davies,[1] Nicola J Downer,[2] Fergus V Gleeson,[1] Timothy Q Howes,[4] Tom Treasure,[5] Shivani Singh,[4] Gerrard D Phillips,[6] on behalf of the British Thoracic Society Pleural Disease Guideline Group

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[1]Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, UK
[2]Department of Respiratory Medicine, King's Mill Hospital, Sutton-in-Ashfield, UK
[3]Department of Respiratory Medicine, The Royal Liverpool University Hospital, Liverpool, UK
[4]Department of Respiratory Medicine, Colchester General Hospital, Colchester, UK
[5]Cardiothoracic Unit, Guy's Hospital, London, UK
[6]Department of Respiratory Medicine, Dorset County Hospital NHS Foundation Trust, Dorchester, UK

Correspondence to
Dr Najib Rahman, Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford OX3 7LJ, UK;
naj_rahman@yahoo.co.uk

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INTRODUCTION

Thoracoscopy under local anaesthetic and intravenous sedation, also known as local anaesthetic thoracoscopy, medical thoracoscopy or pleuroscopy, is increasingly being performed by chest physicians in the UK. In 1999, 11 centres across the UK offered a local anaesthetic thoracoscopy service, increasing to 17 centres in May 2004[1] and 37 centres in 2009 (Dr N Downer, personal communication). This document, which will use the term 'local anaesthetic thoracoscopy', aims to consider the following issues and to make appropriate recommendations on the basis of evidence where available:

- The need for a local anaesthetic thoracoscopy service in the UK.
- Evidence for use of local anaesthetic thoracoscopy as a diagnostic and therapeutic tool.
- The conditions and patients in whom local anaesthetic thoracoscopy could be considered.
- Levels of competence in local anaesthetic thoracoscopy.
- Practical aspects of performing the procedure.

Creation of this guideline followed the Appraisal of Guidelines Research and Evaluation/Scottish Intercollegiate Guidelines Network (AGREE/SIGN) methodology of evidence assessment and integration (see introduction to pleural disease guidelines).

THE NEED FOR A LOCAL ANAESTHETIC THORACOSCOPY SERVICE IN THE UK

Is there a need for a physician-based local anaesthetic thoracoscopy service in the UK? The majority of local anaesthetic thoracoscopy is carried out in the context of an undiagnosed exudative pleural effusion, the commonest cause of which is malignancy.[2] This section of the document will therefore focus mainly on local anaesthetic thoracoscopy in the context of malignant disease.

The increasing burden of pleural disease

Malignant pleural effusion is a common clinical problem. Although the incidence of lung cancer in the UK is falling, the incidence of other cancers is rising. With increasing life expectancy in an ageing population and at current cancer incidence rates, an additional 100 000 cases of cancer per year are expected by 2025.[3] Up to 15% of patients who die with malignancy have a pleural effusion at autopsy.[4] Studies suggest that exudative effusions are caused by malignancy in a large number of cases (42–77%).[5]

Cases of mesothelioma are due to increase until 2020.[6] The annual number of deaths from mesothelioma continues to climb (from 153 deaths in 1968 to 1848 in 2001). The death rate is predicted to peak at around 2450 deaths per year in 10 years' time.[7] It is predicted that 65 000 patients will die of mesothelioma between 2001 and 2050.[7]

There are no epidemiological studies of the incidence/prevalence of malignant pleural effusion in the UK. The annual incidence in the USA is estimated to be 250 000 cases[5 8]; extrapolating this, one might estimate there to be 50 000 new cases of malignant pleural effusion per year in the UK. This would translate to one new case per 1000 population per year. An average district general hospital serving a population of 250 000 might therefore expect to diagnose and treat approximately 250 new cases of malignant pleural effusion annually. Of these predicted 250 cases, only 60% will be diagnosed by pleural aspiration (see later) and only 60–80% will achieve a successful first pleurodesis via an intercostal drain. In both of these instances, patients may benefit from local anaesthetic thoracoscopy. An improved service for patients with malignant pleural disease, either from primary pleural carcinoma or from metastases from other organ sites, is therefore required.

► **Malignant pleural effusion represents an increasing burden of disease both to patients and to healthcare resources. (D)**

EVIDENCE FOR THE USE OF LOCAL ANAESTHETIC THORACOSCOPY

Diagnostic yield of local anaesthetic thoracoscopy in the investigation of suspected pleural malignancy

A significant number of cases of pleural effusion are undiagnosed after simple diagnostic pleural aspiration.[2] Pooled data from a total of 1370 patients suggests that a positive cytological diagnosis of malignancy may be obtained from a single diagnostic pleural aspiration in 60% of cases.[2] A second sample modestly increases the diagnostic yield (by around 15%) but a third sample is non-contributory.[2] Pleural fluid cytology has an even poorer diagnostic yield in mesothelioma, in which a positive result is obtained in only 32% of cases.[9]

Traditionally, 'blind' pleural biopsy (non-image-guided pleural biopsy, also known as closed pleural biopsy or Abrams needle biopsy) has been the next step in investigating cytology negative exudative

pleural effusions of unknown cause. This procedure is relatively cheap and readily accessible and is still used in many institutions. However, there is increasing evidence that 'blind' pleural biopsy is less sensitive in the diagnosis of malignant pleural disease than CT-guided pleural biopsy or local anaesthetic thoracoscopy. This is understandable when one considers that direct visualisation of the pleura in malignancy often reveals patchy abnormalities with disease affecting the more dependent part of the pleura near the diaphragmatic surface. In malignant effusion, use of 'blind' pleural biopsy increases the diagnostic yield above pleural fluid cytology alone by 7–27%.[2] For mesothelioma, addition of 'blind' pleural biopsy to fluid cytology increases the diagnostic yield in total to 50%.[10] Alternative diagnostic strategies have therefore been investigated, including ultrasound and CT-guided pleural biopsy. In a randomised controlled trial comparing diagnostic rates in CT-guided versus 'blind' pleural biopsy for suspected malignancy, 'blind' pleural biopsy had a sensitivity of 47% compared with 87% for CT-guided biopsy.[11] This translates to one pleural biopsy being avoided for every 2.5 CT-guided biopsies undertaken.

Contrast-enhanced thoracic CT scanning is the next recommended investigation of choice in cytology negative pleural effusion.[2] Areas of pleural thickening or nodularity may be identified and subsequently biopsied under image guidance with a good diagnostic yield.[11] However, abnormal pleural appearances are not always seen on thoracic CT scans and biopsies are sometimes negative. Where a diagnosis is obtained, further intervention is usually required to treat and control the effusion (see below). Furthermore, although thoracic CT scanning followed by image-guided biopsy is effective in diagnosis, radiology departments in many hospitals are overstretched and there is variable access to this service.

Local anaesthetic thoracoscopy allows direct visual assessment of the pleura and subsequent biopsy of visually abnormal areas, hence maximising diagnostic yield. A total of 22 case series have reported diagnostic yield of local anaesthetic thoracoscopy for malignant disease.[12–33] Pooling results from all these studies, thoracoscopy has a 92.6% diagnostic sensitivity for malignant pleural disease (1268/1369, 95% CI 91.1% to 94.0%). Pooling results from only those eight studies in which a prior 'blind' pleural biopsy was negative,[12 15–17 24 25 31 33] local anaesthetic thoracoscopy had a similarly high sensitivity of 90.1% (334/337, 95% CI 86.6% to 92.9%).

Several large case series have reported high diagnostic sensitivity and specificity in the diagnosis of malignant pleural effusion using video-assisted thoracoscopic surgery (VATS)[34 35] (see Harris *et al*[35] for review of case series before 1995). While there are no studies directly comparing medical with surgical (VATS) thoracoscopy, the above evidence suggests that local anaesthetic thoracoscopy has a similarly high diagnostic rate in malignant pleural effusion. Examining the largest of these case series in more detail, Hansen *et al*[14] retrospectively examined the diagnostic yield of local anaesthetic thoracoscopy in 147 patients, 136 of whom had pleural effusion which was cytology and microbiology negative on three samples. The overall diagnostic sensitivity was 90.4% with a sensitivity of 88% and a specificity of 96% for malignant disease. Menzies *et al*[15] prospectively evaluated local anaesthetic thoracoscopy in 102 patients, 86 of whom had undiagnosed pleural effusion after pleural aspiration and 'blind' pleural biopsy. The overall sensitivity for diagnosis of malignancy was 96%, a figure comparable with that quoted for CT-guided biopsy (87% sensitivity).[11] In a retrospective series of 149 cases, Blanc *et al*[12] showed that in 66 cases of 'inflammation' diagnosed at blind pleural biopsy, 32 (48%) were re-diagnosed at thoracoscopy (including 16 cases of malignant mesothelioma, 13 cases of carcinoma and 3 cases of tuberculosis).[15]

The diagnostic yield of local anaesthetic thoracoscopy in case series of malignant mesothelioma appears to be equally good. In a retrospective case series of 188 patients with malignant mesothelioma, the sensitivity of thoracoscopic biopsies is reported as >90%.[13] This high diagnostic rate of local anaesthetic thoracoscopy in malignant mesothelioma is of particular importance, given the even lower diagnostic yield from pleural fluid cytology and blind pleural biopsy in this disease and the importance of avoiding multiple pleural procedures.[36]

The 'semi-rigid' or flexible thoracoscope is a relatively new innovation in the field of pleural disease. Four studies accurately report the diagnostic rate for malignancy,[16 21 23 24] which combined give a diagnostic sensitivity for malignant pleural disease of 96/113 (85.0%, 95% CI 78.4% to 91.5%).

With increasing pressure on services to rapidly achieve diagnosis and treatment in patients with possible malignancy, local anaesthetic thoracoscopy offers a high diagnostic yield for malignancy and a therapeutic procedure in the same sitting (see below). Blind pleural biopsy after initial negative cytology is a cheap and readily available technique, but it is associated with a substantially lower diagnostic yield and its use may lead to delay in diagnosis and treatment. Where the option exists to access techniques with a higher diagnostic yield earlier in the patient journey, these may help to decrease the time taken to achieve diagnosis and treatment.

- **The currently available data support local anaesthetic thoracoscopy as one of the techniques with the highest diagnostic yield in aspiration cytology negative exudative pleural effusion. (D)**
- **The efficacy of rigid local anaesthetic thoracoscopy in this regard appears to be as high as for video-assisted thoracoscopic surgery (VATS). (D)**

Local anaesthetic thoracoscopy as a therapeutic procedure

When a diagnosis of malignancy is made using pleural fluid cytology, blind pleural biopsy or image-guided biopsy, management of symptomatic pleural effusion usually requires further intervention. This most commonly takes the form of either chest drain insertion and subsequent 'medical' pleurodesis[37] or referral for a VATS pleurodesis. 'Medical' pleurodesis via a chest drain using various agents succeeds in approximately 60% of patients,[37] with the remainder requiring further intervention, often necessitating further hospital admissions or a surgical referral. This represents an extra burden to both the patient and the healthcare service in terms of waiting time, days spent in hospital and invasive procedures. Local anaesthetic thoracoscopy offers diagnostic and therapeutic procedures in a single sitting, which is of particular relevance to mesothelioma where minimising thoracic procedures may be important with the associated risk of biopsy tract invasion and the possible need for biopsy site radiotherapy.[36 38–40]

Pleurodesis by talc insufflation (talc poudrage) can be undertaken during local anaesthetic thoracoscopy if the pleura appears abnormal on direct inspection. Eleven studies have assessed the efficacy of talc poudrage by local anaesthetic thoracoscopy in patients with malignant pleural effusion only[41–51] (a further six studies[12 18 28 52–54] included patients with malignant and benign causes of pleural effusion), including two randomised controlled trials. Interpretation of the efficacy rate of talc poudrage is complicated by the considerable heterogeneity in how each of these studies assessed 'success' rate. However, pooling data from

all these studies suggests that the efficacy of talc poudrage at 1 month in patients with malignant disease only (radiological outcome) is around 84% (645/765, 95% CI 81.7% to 86.9%). If studies including both benign and malignant causes of effusion are included, the radiological success rate at 1 month of talc poudrage pleurodesis is unchanged at 85% (839/982, 95% CI 83.2% to 87.6%). However, analysing combined data from the two randomised trials only suggests a lower success rate than this at 1 month (158/237, 67%).

Direct comparison of talc slurry pleurodesis with talc poudrage for malignant pleural effusion has been the subject of a Cochrane review. The RR of non-recurrence of pleural effusion was calculated as 1.19 in favour of talc poudrage via thoracoscopy, increasing to 1.68 when a variety of other sclerosants were used. However, the largest randomised study by Dresler *et al*[43] in 482 patients was published after this Cochrane review and showed equal success rates for poudrage and slurry pleurodesis (60% for poudrage vs 52% for slurry, p=0.1). Subgroup analysis of those patients without trapped lung (ie, where pleurodesis was technically achievable) suggested a slight benefit of talc poudrage (82% poudrage vs 71% slurry, p=0.045) with further benefit in patients with lung or breast carcinoma (82% poudrage vs. 67% slurry). Taken together, the current evidence suggests that talc poudrage is a highly effective method of pleurodesis which is at least equivalent to talc slurry with possibly increased efficacy in certain disease subgroups. Further targeted studies in these subgroups are needed.

The optimal length of hospital stay after local anaesthetic thoracoscopy poudrage is unknown. The mean length of stay of patients after the procedure across eight case series of local anaesthetic thoracoscopy in a total of 361 patients was 4.6 days.[49–52 55–58]

- **Local anaesthetic thoracoscopy provides a high diagnostic yield and effective therapeutic pleurodesis in a single procedure. (C)**

Safety of local anaesthetic thoracoscopy

Many patients with undiagnosed pleural effusion are unsuitable for surgical diagnostic and therapeutic strategies such as VATS procedures due to comorbidity, limited survival and inability to tolerate general anaesthetic. Local anaesthetic thoracoscopy under intravenous sedation offers these patients a reasonably high likelihood of diagnosis and pleurodesis in a single procedure that is well tolerated.

Overall, local anaesthetic thoracoscopy is a safe procedure. Combining data from 47 studies in which complications from local anaesthetic thoracoscopy were reported,[12–17 19 22–26 28–31 42–45 47–72] death occurred in 16/4736 cases (0.34%, 95% CI 0.19% to 0.54%). Of these studies, 28 were of diagnostic thoracoscopy alone[13–17 19 22–26 29–31 55 56 58–60 62–66 68 69 72 73] in which the combined mortality was 0/2421 (0%, 95% CI 0% to 0.15%). The 19 studies involving talc poudrage[12 28 42–45 47–54 57 61 67 70 71] gave a combined mortality of 16/2315 (0.69%, 95% CI 0.40% to 1.12%). A major contribution to this mortality (9 deaths out of 16) was from a large randomised study of talc poudrage conducted in the USA using non-graded talc.[43]

Major complications (empyema, haemorrhage, port site tumour growth, bronchopleural fistula, postoperative pneumothorax or air leak and pneumonia) were reported in the same 47 studies and occurred in 86/4736 cases (1.8%, 95% CI 1.4% to 2.2%). Where minor complications (subcutaneous emphysema, minor haemorrhage, operative skin site infection, hypotension during procedure, raised temperature, atrial fibrillation) were reported (31 studies[12–17 19 23 42 44 47–60 62–66 68 73]), these occurred in 177/2411 procedures (7.3%, 95% CI 6.3% to 8.4%).

The complication rate of talc poudrage is probably related to both the dose and type (graded versus non-graded[74]) of talc used (see the practical procedure guide in the online appendix). In a large randomised trial of talc poudrage for malignant pleural effusion,[43] 9/222 poudrage patients (4.1%) and 7/240 patients (2.9%) died from presumed talc-associated respiratory failure and acute respiratory distress syndrome (ARDS) (χ^2 test, 1df=0.3, p=0.61). All these cases were treated with non-graded (USA) talc. A recent large multicentre cohort study using exclusively graded talc found no instances of ARDS or death related to talc poudrage at local anaesthetic thoracoscopy in 558 patients.[75]

- **Local anaesthetic thoracoscopy is a safe procedure. (D)**
- **Where talc poudrage is to be conducted, graded talc should be used. (C)**

Use in other conditions

Tuberculosis

'Blind' pleural biopsy is a robust diagnostic tool in suspected tuberculosis (TB) pleuritis as this condition affects the pleura diffusely and is cheap and widely available. High diagnostic sensitivity has been reported in areas of high TB prevalence.[76] 'Blind' pleural biopsy is therefore a good initial choice of diagnostic strategy in suspected TB pleuritis, particularly in areas of high TB prevalence.

As a diagnostic tool, local anaesthetic thoracoscopy has a higher diagnostic yield than blind pleural biopsy for TB pleuritis. Six studies[25 26 29–31 76] have reported the diagnostic sensitivity of local anaesthetic thoracoscopy for TB pleuritis including one direct comparison with 'blind' (Abrams) biopsy[76] (see below). Five of these studies were conducted in areas of low prevalence for TB,[25 26 29–31] with the other[76] conducted in South Africa. Pooling the results of the five low prevalence area studies,[25 26 29–31] local anaesthetic thoracoscopy had a diagnostic yield of 93.3% (42/45). In the prospective trial comparing local anaesthetic thoracoscopy with Abrams biopsy in an area with a high TB prevalence,[76] thoracoscopy was found to have a combined culture/histology sensitivity of 100% compared with 79% for 'blind' pleural biopsy. Therefore, the technique with the highest diagnostic rate for TB pleuritis on the basis of published evidence is local anaesthetic thoracoscopy. However, since blind pleural biopsy has high sensitivity and is likely to be more cost-effective as an initial diagnostic procedure, it will often be the procedure of first choice, depending on service availability, operator skill, workload, the pretest probability of TB and the prevalence within the population. If 'blind' pleural biopsy is unsuccessful in suspected TB pleuritis, thoracoscopy is recommended as the next diagnostic step.

- **Local anaesthetic thoracoscopy has a high yield for TB pleuritis and a greater yield than blind pleural biopsy in high prevalence TB areas. (D)**
- **If blind pleural biopsy is non-diagnostic, local anaesthetic thoracoscopy is a reasonable next diagnostic step. (D)**

Empyema

Local anaesthetic thoracoscopy may be useful for the treatment of pleural infection, allowing division of septations and adhesions and facilitating accurate tube placement and drainage. It has been used in Europe as a primary treatment strategy for treating empyema. Three studies are reported in the literature on the use

of local anaesthetic thoracoscopy for the treatment of pleural infection.[53 59 68] All of these are non-comparator case series (one prospective) and in combination show a high 'success rate' of treatment (131/143, 91.6%) and no complications (Grade D).

However, local anaesthetic thoracoscopy is not currently used in the UK either as primary or rescue therapy for pleural infection. Thoracic surgical intervention is the current treatment of choice for patients not responding to initial medical therapy (see guidelines on pleural infection). Large prospective randomised comparator trials are needed to elucidate the exact role of local anaesthetic thoracoscopy in this context. The limited evidence above is unlikely to change current UK practice, although it may be a technique which is used in the future with collaboration between a medical thoracoscopist and a thoracic surgeon.

Pneumothorax

In Europe, talc poudrage at local anaesthetic thoracoscopy is a common treatment for primary spontaneous pneumothorax. Definitive treatment for pneumothorax is not usually considered in the UK after the first episode of pneumothorax, except in specific circumstances such as occupational reasons or bilateral pneumothoraces (see guideline on pneumothorax). One case series from Europe reported good long-term results from talc poudrage pleurodesis using 'medical' thoracoscopy (performed under general anaesthetic) in patients with a persistent air leak (>7 days) or recurrent pneumothorax, demonstrating a 93% success rate (lack of further ipsilateral pneumothorax) over a mean of 5 years of follow-up.[70] One randomised study compared talc poudrage pleurodesis with intercostal tube drainage as initial therapy for primary spontaneous pneumothorax, demonstrating superiority of talc poudrage (recurrence rate 3/59, 5.1%) over the intercostal tube drainage group (recurrence rate 16/47, 34%).[71] Talc poudrage pleurodesis therefore appears to be an effective treatment for patients with primary spontaneous pneumothorax. However, in the UK, surgical management of primary spontaneous pneumothorax is considered the definitive treatment strategy and is associated with low operative mortality and excellent results. Additional procedures of blebectomy, pleurectomy and abrasion pleurodesis are usually possible only under single lung ventilation and are normally conducted under general anaesthesia, within the remit of thoracic surgery only. Physician-led thoracoscopy may develop in the future as a treatment strategy for these patients, but further evidence defining its role compared with the gold standard of surgical management is required. In addition, talc pleurodesis is likely to be very painful in patients with normal parietal pleural surfaces (such as those with primary pneumothorax) and therefore deep sedation or general anaesthesia may be required for this treatment.

Secondary pneumothorax in patients with chronic obstructive pulmonary disease (COPD) heralds increased mortality and often requires prolonged hospital admission.[77] These patients are often poor surgical candidates because of poor lung function and are at high risk from general anaesthesia; there is no evidence base on which to determine treatment in this very difficult group. Talc slurry via a chest drain is often advocated, but such patients may also be treated by local anaesthetic thoracoscopy. There is a single series[78] (n=41) assessing the efficacy of talc poudrage pleurodesis in COPD-related pneumothorax (average forced expiratory volume in 1 s (FEV_1) 41% predicted), demonstrating a 95% success rate for pleurodesis after an average follow-up of 3 years. Four patients (9.8%) died within 30 days of the procedure and seven (17%) experienced ongoing air leak for >7 days.

- **Talc poudrage pleurodesis may be an effective treatment for both primary and secondary pneumothorax (D). However, the current definitive treatment strategy for these patients is thoracic surgery (video-assisted thoracoscopic surgery or mini-thoracotomy with pleural abrasion pleurodesis with or without lung resection).**
- **If surgery is deemed unsuitable because of the associated significant risks in some patients with secondary pneumothorax, local anaesthetic thoracoscopy may be considered if undertaken by experienced practitioners.**

Other indications

Lung biopsy

Medical thoracoscopic 'pinch' lung biopsy is practised in some parts of Europe to aid diagnosis in the case of diffuse interstitial lung disease or diffuse shadowing in immunocompromised patients. There are three case series[62 66 72] (one prospective[72]) reporting the results of such 'pinch' lung biopsies undertaken during local anaesthetic thoracoscopy. A total of 148 patients were studied across these three studies, 87 with interstitial lung disease and the remainder were immunocompromised. No deaths were reported, with a procedure-associated major complication rate of 5/148 (3%). Overall, the 'diagnostic rate' in these studies (which was taken in each study to mean a result from the lung biopsy which changed patient management) was high (135/148, 91%) (grade D).

In view of current UK practice of the diagnosis and management of interstitial lung disease and of diffuse parenchymal shadowing in immunocompromised patients, local anaesthetic thoracoscopy cannot currently be recommended for these indications in the UK. Lung biopsy for the diagnosis of such parenchymal lung disease is currently undertaken using thoracic surgical techniques where appropriate, if bronchoscopic transbronchial biopsy is negative or considered inappropriate. Changes in diagnostic algorithms for diffuse interstitial lung disease in the future may make local anaesthetic thoracoscopy a useful and more widespread procedure, but would be confined to higher level physician operators.

Similarly, thoracoscopic sympathectomy is performed in Europe but not in the UK by physician thoracoscopists. However, changes in work and referral patterns in the future may make this a potential application in the UK. These techniques would again be confined to operators with substantial experience (see section on operator levels below).

INDICATIONS FOR LOCAL ANAESTHETIC THORACOSCOPY

This section of the guideline addresses clinical considerations for patients who are suitable for or may be referred for a local anaesthetic thoracoscopy. This part of the document has been drafted on the basis of expert opinion from physician local anaesthetic thoracoscopists from the UK.

General

Local anaesthetic thoracoscopy should generally only be undertaken in patients with a radiologically confirmed pleural effusion (although advanced operators may induce pneumothorax). It should usually only be undertaken in patients with good performance status (WHO status 0, 1 or 2). However, any dyspnoea secondary to the effusion will be relieved by the procedure, so breathlessness alone is not necessarily a contraindication. Local anaesthetic thoracoscopy should generally be undertaken in those in whom survival is expected to be reasonable; it is not appropriate in terminally ill patients.

Diagnostic procedures of any sort, including local anaesthetic thoracoscopy, should only be performed in patients in whom a tissue diagnosis will affect management. Local anaesthetic thoracoscopy should be reserved for those patients in whom the diagnostic/therapeutic benefit is judged to be worth the burden of an invasive procedure and subsequent hospital stay. In practical terms, the performance status of the patient and the predicted prognosis are likely to dictate this.

It is expected that the majority of patients undergoing local anaesthetic thoracoscopy will have had a thoracic CT scan first.

The provision of 'on table' thoracic ultrasound prior to local anaesthetic thoracoscopy is not a requirement to perform the procedure. However, it is likely to increase safety, prevent inaccurate port site entry and decrease the number of 'complicated' thoracoscopies (eg, if a heavily septated effusion is seen, only a higher level operator would proceed). In two case series totalling 707 patients,[22 73] the routine use of preprocedure ultrasound resulted in only one (0.1%) inaccurate entry site. Preprocedure thoracic ultrasound scanning should therefore be used where possible and where there are adequately trained staff to perform the scan.

Fitness for procedure

Patients should be fit enough to undergo the procedure. The majority of patients will gain symptomatic relief from pleural effusion drainage undertaken during thoracoscopy. Dyspnoea due to pleural effusion alone is therefore not a contraindication to the procedure per se.

The procedure involves intravenous sedation and therefore a reasonable level of oxygen saturation (>90% with additional oxygen during the procedure) is required. A single small study has assessed respiratory gas changes during local anaesthetic thoracoscopy[60] using intravenous hydrocodone and boluses of pethidine and midazolam in patients who were given oxygen during the procedure. This study demonstrated minor changes only in carbon dioxide and oxygen tensions (P_{CO_2} and P_{O_2}) during the procedure (mean±SD change in P_{CO_2} 1.76±0.71 kPa; mean±SD change in P_{O_2} 0.61±0.43 kPa).

Patients must be able to tolerate lying flat/on their side for the duration of the procedure. Substantial dyspnoea on lying flat/in the lateral decubitus position is not per se a contraindication to thoracoscopy as drainage of fluid at the beginning of the procedure is likely to alleviate this.

Where concerns exist about sedating very dyspnoeic patients, particularly if two drugs are to be used, clinicians may wish to seek anaesthetic advice.

Consent

Written informed consent is mandatory where the patient is competent and should only be obtained by a member of staff trained in the procedure or adequately trained to take consent according to General Medical Council guidelines. Written information should be provided before the consent process.

Absolute contraindications

The following are absolute contraindications:

- Lung adherent to the chest wall throughout the hemithorax.
- Hypercapnia or severe respiratory distress.
- Uncontrollable cough (making safe entry and movement of thoracoscopes within the chest hazardous).
- Lack of informed consent in a competent patient.

Relative contraindications

The following are relative contraindications:

- Very severe obesity may make the procedure technically more difficult and may prevent entry into the thoracic cavity due to inadequate cannula length.
- As in the British Thoracic Society bronchoscopy guidelines, any reversible condition (eg, infection, airways disease) should be fully treated before the procedure. Caution will be required in patients with certain significant comorbid conditions (eg, ischaemic heart disease, recent myocardial infarction (for which the procedure should be delayed by at least 4 weeks after the initial event), clotting dysfunction, renal failure and immunocompromise), and such conditions should be addressed prior to the procedure just as they are prior to bronchoscopy.[33]
- A high likelihood of trapped lung is a contraindication to therapeutic thoracoscopy as this suggests a successful pleurodesis is very unlikely.
- The known presence of an obstructing central airway tumour is a contraindication as, in such instances, bronchoscopy with or without intervention is the investigation/treatment of choice.

Place of local anaesthetic thoracoscopy in the diagnostic pathway

The published BTS guideline on the investigation of unilateral pleural effusion provides a scheme for the order of diagnostic strategies to be used.[2] In patients with an exudative pleural effusion where a single (and in some cases second[79]) diagnostic pleural aspiration is negative, the size of the effusion will guide further investigation. In those in whom an effusion of more than one-third of the hemithorax is present, a CT scan should be obtained. This should guide the selection of the next investigation step which is likely to be either CT-guided biopsy or thoracoscopy, either local anaesthetic or surgical (VATS). Factors that will decide how the patient proceeds along the diagnostic and therapeutic pathway will include performance status, life expectancy, whether or not a suitable target for CT-guided biopsy is present, the size of the pleural effusion, the likelihood that the lung will re-expand, consideration of whether a pleurodesis is indicated and, if so, the pros and cons of talc slurry versus talc poudrage in the individual case.

Clearly, poor performance and/or limited life expectancy are factors that will argue against the use of thoracoscopy, whether local anaesthetic or VATS. A clear target for CT-guided biopsy may lead to selection of this technique as the next investigation after pleural aspiration but, if a talc poudrage pleurodesis is intended, the physician may still opt for thoracoscopy instead. The size of the pleural effusion will guide whether or not local anaesthetic thoracoscopy is possible, but no hard and fast rule as to size can be applied as the decision will depend on the individual case and the level of operator training and experience, with more experienced physicians undertaking the procedure on smaller effusions than those who are less experienced. In the case of a small or absent pleural effusion, thoracoscopy may involve the induction of a pneumothorax and would therefore usually be carried out by more experienced operators (eg, level II operators, see below).

'Blind' closed pleural biopsy may be used in institutions in which other further diagnostic techniques are not readily available locally. It should be noted that this technique is associated with a significantly poorer diagnostic yield compared with image-guided or thoracoscopic procedures, except in the case of suspected TB pleuritis. Overall, blind closed pleural biopsy should therefore only be considered if TB is a possible diagnosis and the patient lives in a high TB prevalence area. All

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diagnostic techniques in the investigation of exudative pleural effusions should be subject to routine clinical audit to include diagnostic yield and delay caused by missed diagnoses and the need for further procedures. Where any technique is found to achieve low diagnostic rates or results in diagnostic or treatment delays, the procedure should be abandoned in favour of strategies with a higher diagnostic yield and less treatment delay.

Local anaesthetic thoracoscopy should not in general be considered a first-line investigation where more simple diagnostic strategies (eg, aspiration cytology) have not yet been tried. However, as the procedure offers the opportunity for both diagnosis and therapy in a single sitting, it is not unreasonable (especially if the pretest probability of malignant mesothelioma is high) to use thoracoscopy early in the diagnostic investigation to prevent multiple pleural procedures.

While local anaesthetic thoracoscopy is usually undertaken in cytology negative patients, it may still be appropriate in the case of a confirmed cytology positive malignant effusion. A positive cytological diagnosis on pleural fluid may be sufficient to guide further management, but where cytology is only able to confirm the presence of 'suspicious' cells or in patients in whom accurate histology will change treatment (eg, small cell lung cancer, breast cancer, differentiating adenocarcinoma from mesothelioma), local anaesthetic thoracoscopy may be indicated.

In cases of highly chemotherapy sensitive tumours (eg, lymphoma, small cell lung cancer), treatment of the underlying cancer is likely to result in resolution of pleural effusion without recourse to drainage or pleurodesis. Local anaesthetic thoracoscopic poudrage for pleural fluid control is therefore not recommended where such a diagnosis is established on the basis of other investigations, and where chemotherapy is planned.

A CT scan is not an absolute requirement prior to thoracoscopy but is strongly recommended. A thoracic CT scan prior to the procedure allows accurate identification of pleural nodularity in the presence of pleural fluid.[2] It may also permit identification of an underlying obstructing bronchial carcinoma where the appropriate next step is bronchoscopy. In addition, a prior thoracic CT scan allows accurate pretreatment staging. The order of investigations will depend on the details of the individual cases and on local resource provision.

The medical thoracoscopist should have the facility to discuss selected cases with local cardiothoracic centres to establish whether a surgical procedure (VATS/thoracotomy) or a local anaesthetic thoracoscopy is the optimal treatment strategy for each individual case. This will involve a discussion of the balance between the risks and benefits of the two approaches in the individual patient.

LEVELS OF COMPETENCE IN LOCAL ANAESTHETIC THORACOSCOPY

This section defines three levels of medical thoracoscopic practice that are current in European countries and are likely to be reflected in UK respiratory medicine as local anaesthetic thoracoscopy becomes more widely practised. Information specifying the required training to gain competence at each level in local anaesthetic thoracoscopy is not specified here but will be available after consultation with the appropriate training committees at a later date. Annual audit of diagnostic/complication rates is encouraged for all procedures.

Level I

This includes basic diagnostic and therapeutic techniques and is likely to be the level of competence at which the majority of district general physicians practise. A medical thoracoscopist practising at this level of competence should be able to:

1. manage patients who have large pleural effusions; however, in some instances, and as experience increases, a level I thoracoscopist may undertake the procedure in patients with smaller effusions;
2. biopsy the parietal but not the visceral pleura;
3. undertake therapeutic talc insufflation.

A level I thoracoscopist should be able to supervise training, subject to having performed sufficient unsupervised and audited thoracoscopies him/herself.

Level II

This is the level of competence practised in the setting of a regional service and will involve more experienced practitioners within a unit with a major interest in pleural disease. Such operators should be competent in (1), (2) and (3) plus some of the other procedures listed below:

1. level I techniques;
2. undertaking local anaesthetic thoracoscopy in patients with small/no pleural effusion (pneumothorax induction);
3. visceral pleural biopsy;
4. pinch lung biopsy;
5. lysis of adhesions and lavage in the setting of a loculated or infected pleural space;
6. talc pleurodesis in patients with secondary pneumothorax unsuitable for general anaesthetic/VATS;
7. in some cases, expertise in other techniques such as sympathectomy.

Level III

This level covers all VATS techniques (eg, lung resection) and is currently the province of the thoracic surgeon. It is beyond the remit of this document.

Competing interests No member of the Guideline Group is aware of any competing interests.

Provenance and peer review The draft guideline was available for online public consultation (July/August 2009) and presented to the BTS Winter Meeting (December 2009). Feedback was invited from a range of stakeholder institutions (see Introduction). The draft guideline was reviewed by the BTS Standards of Care Committee (September 2009).

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Pleural procedures and thoracic ultrasound: British Thoracic Society pleural disease guideline 2010

Tom Havelock,[1] Richard Teoh,[2] Diane Laws,[3] Fergus Gleeson,[4] on behalf of the BTS Pleural Disease Guideline Group

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[1]Wellcome Trust Clinical Research Facility, Southampton General Hospital, Southampton, UK
[2]Department of Respiratory Medicine, Castle Hill Hospital, Cottingham, East Yorkshire, UK
[3]Department of Thoracic Medicine, Royal Bournemouth Hospital, Bournemouth, UK
[4]Radiology Department, Churchill Hospital, Oxford, UK

Correspondence to
Dr Tom Havelock, Wellcome Trust Clinical Research Facility, Southampton General Hospital, Southampton SO16 6YD, UK; t.havelock@soton.ac.uk

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BACKGROUND

In hospital practice, pleural aspiration (thoracocentesis) and chest drain insertion may be required in many different clinical settings for a variety of indications. Doctors in most specialities will be exposed to patients requiring pleural drainage and need to be aware of safe techniques. There have been many reports of the dangers of large-bore chest drains and it had been anticipated that, with the previous guidelines, better training and the advent of small-bore Seldinger technique chest drains, there would have been an improvement. Unfortunately the descriptions of serious complications continue, and in 2008 the National Patient Safety Agency (NPSA) issued a report making recommendations for safer practice.[1] These updated guidelines take into consideration the recommendations from this report and describe the technique of pleural aspiration and Seldinger chest drain insertion and ultrasound guidance. Much of this guideline consists of descriptions of how to do these procedures but, where possible, advice is given when evidence is available.

TRAINING

► **All doctors expected to be able to insert a chest drain should be trained using a combination of didactic lecture, simulated practice and supervised practice until considered competent. (✓)**

Before undertaking an invasive pleural procedure, all operators should be appropriately trained and have been initially supervised by an experienced trainer. Many of the complications described in the NPSA report were the result of inadequate training or supervision. A recent survey of UK NHS Trusts showed that the majority did not have a formal training policy for chest drain insertion in 2008.[2]

Studies of clinical practice have shown that there is a wide variation in the knowledge and skills of doctors inserting chest drains. In a published study[3] where doctors were asked to indicate where they would insert a chest drain, 45% indicated they would insert the drain outside of the safety triangle, with the majority of incorrect answers being too low. Knowledge of the correct position was higher in the group with cardiothoracic surgery experience and higher in doctors with competence to insert drains without supervision.

Training should include a theoretical component describing the risks and technique, as outlined in this document, prior to assessed manikin practice and finally supervised procedure until considered competent. In the UK it is currently part of the curriculum for core medical training and trainees should be expected to describe the procedure and complications in an examination. The trainee should ensure each procedure is documented in their log book and signed by the trainer. A Directly Observed Practice (DOP) assessment should be completed in support of this.

Studies of training involving didactic lectures, manikin practice and following protocols, including use of sedation and anaesthesia, have shown the risk of complications and patient pain and anxiety can be reduced[4] and trainee knowledge and confidence in the procedures may be increased.[5]

The use of simulators has been compared with the use of animal models for blunt dissection as part of ATLS training. Forty-one trainees and 21 experts were asked to evaluate a simulator compared with an animal model and they were found to be equivalent in most areas apart from anatomical landmarks where the simulator was superior and the blunt dissection where the animal model was superior.[6]

Training for thoracic ultrasound should follow the principles set out by the Royal College of Radiologists and is described in greater detail later in this document.

These guidelines will aid the training of junior doctors in these procedures and should be readily available for consultation by all doctors likely to be required to carry out pleural aspiration or chest tube insertion. An algorithm for the insertion of a chest drain is shown in figure 1.

PRE-PROCEDURE PREPARATION

Timing of procedures

► **Pleural procedures should not take place out of hours except in an emergency. (✓)**

Complications of most surgical procedures are higher when performed after midnight. Most pleural procedures do not need to be performed as an emergency and therefore should not be carried out overnight except in the case of significant respiratory or cardiovascular compromise. It may be considered in certain circumstances that pleural aspiration is safer than a chest drain.

Aseptic technique

► **Pleural aspirations and chest drains should be inserted in a clean area using full aseptic technique. (✓)**

Empyema and wound site infections are significant complications of pleural procedures.

A large area of skin cleansing should be undertaken using two applications of alcohol-based skin

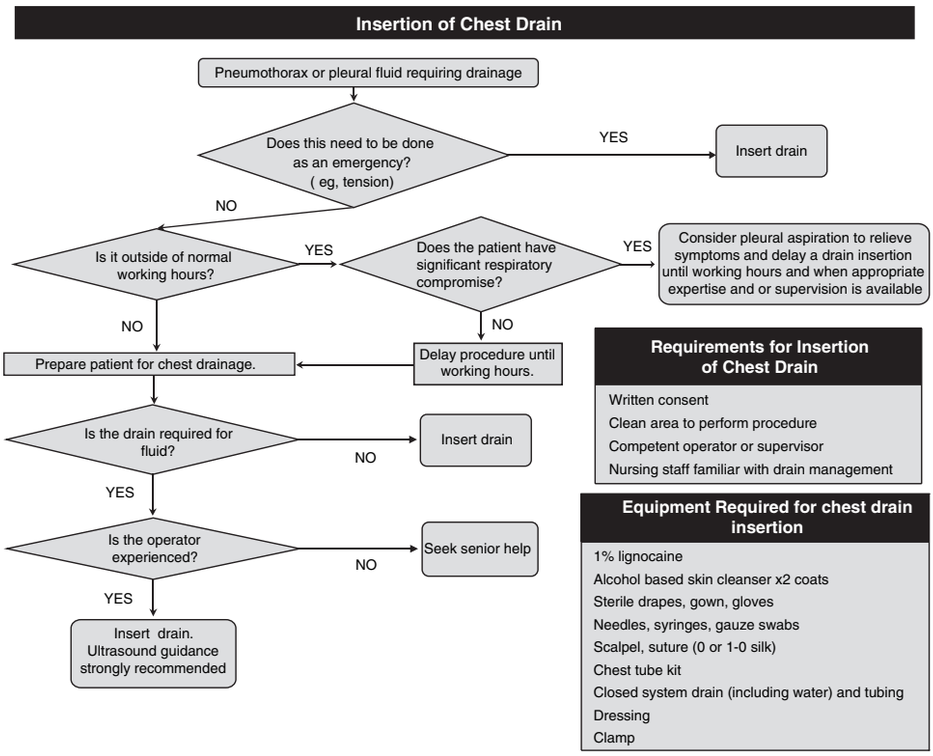

Figure 1 Algorithm for the insertion of a chest drain.

disinfectant (or other if recommended by the local infection control team), allowing it to dry in between applications. The procedure should be carried out in a clean area appropriate for such procedures.

Clotting disorders and anticoagulation

- **Non-urgent pleural aspirations and chest drain insertions should be avoided in anticoagulated patients until international normalised ratio (INR) <1.5. (C)**

Patients known to be receiving anticoagulants or in whom there is a suspected coagulopathy (eg, liver failure) should have their prothrombin time (PT) or international normalised ratio (INR) measured prior to a non-urgent pleural procedure. In the case of a tension pneumothorax, it may be necessary to insert a drain first before correcting an abnormal INR. McVay *et al*[7] retrospectively reviewed 608 cases undergoing paracentesis or pleural aspiration and found that mild coagulopathy, defined as an INR <1.5 or platelet counts 50–99 10^9/l, did not adversely affect the risk of bleeding with a fall in haemoglobin of 2 g/dl occurring in only 3.1% and 0.2% requiring transfusion.

If a patient has abnormal coagulation and requires an invasive pleural procedure, the advice of the local haematologist should be sought regarding the correct action needed to normalise the clotting.

PLEURAL ASPIRATION (THORACOCENTESIS)

Pleural aspiration describes a procedure whereby pleural fluid or air may be aspirated via a system inserted temporarily into the pleural space. This may be for diagnostic purposes (usually removing 20–50 ml fluid) or therapeutic to relieve symptoms. In the literature it is varyingly called thoracocentesis, thoracentesis or pleural aspiration.

Indications

The indications for pleural aspiration are shown in box 1.

Preparation and consent

Before performing a pleural aspiration, operators should ensure documented consent is obtained and that they are either competent or supervised to do the pleural aspiration. They should be aware of the indication for the procedure, whether it is diagnostic or therapeutic and have all equipment ready.

The consent procedure should encompass the indications for the procedure, alternatives to the procedure and the common and serious complications.

Complications

- **The commonest complications from pleural aspiration are pneumothorax, procedure failure, pain and haemorrhage. The most serious complication is visceral injury. These complications should be included in any consent process. (✓)**

A number of factors have been reported to increase the frequency of complications following pleural aspiration. The broadest agreement across the studies examined was that

Box 1 Indications for pleural aspiration

Pneumothorax*
- Spontaneous primary pneumothorax (any size)
- Small secondary spontaneous pneumothorax in patients under 50 years

Malignant pleural effusions*
- Small volume aspiration for diagnosis
- Larger volume aspiration to relieve symptoms of dyspnoea

Pleural effusion associated with sepsis (suspected empyema)*
- Diagnostic for decision to drain

* Refer to specific guidelines for further detail.

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increased operator experience and the use of image guidance reduced the frequency of complications. A fixed effects meta-analysis calculation of the complication frequency across all the studies examined according to these two factors is shown in table 1.

Other factors such as the needle size used and the volume of fluid aspirated have been shown in a few studies to have an effect and are discussed below. Underlying chronic obstructive pulmonary disease[8], previous radiotherapy[9] and previous pleural aspiration[10] have also been suggested as risk factors in individual studies and more evidence is required before recommendations can be made.

In many studies pneumothorax is the most commonly occurring complication following pleural aspiration, but the pathophysiology of post-aspiration pneumothorax is likely to be multifactorial. Some pneumothoraces are undoubtedly caused by lung injury or introduction of air during the procedure. However, Boland *et al*, in a retrospective study of 512 pleural fluid aspirations, found that 17 of the 29 pneumothoraces requiring catheter drainage did not resolve with drainage. They termed this an 'ex vacuo' pneumothorax. All of the 17 patients had malignant parenchymal lung disease. Interestingly, despite the presence of the ex vacuo pneumothorax, 14 of the patients found an improvement of their dyspnoea after the aspiration of their pleural effusion.[11]

The authors concluded that these pneumothoraces occurred due to unexpandable lung underlying the pleural effusion—what many sources refer to as 'trapped lung'. The aspiration of the pleural fluid then causes significantly low pressure within the pleural space and air is drawn in. The mechanism by which this occurs has not been fully determined. Other authors have supported this view.[12]

Ponrartana *et al* confirmed the finding that chest drain insertion as a treatment of an ex vacuo pneumothorax is unlikely to be helpful in decreasing the size of the pneumothorax. They also found that the presence of an ex vacuo pneumothorax in the context of malignant disease is associated with a poor prognosis.[13]

We conclude that, if an ex vacuo pneumothorax occurs after drainage of a pleural effusion due to non-expansile or trapped lung, the pneumothorax should not routinely be drained. Drainage of the pleural effusion if it recurs may bring symptomatic relief. Indwelling pleural catheters may be useful in this context.

Only one case of injury to a solid viscus was found in the context of a cohort or case series,[14] although several examples of other visceral injuries are published in case reports. Despite the low reported frequency, studies of the accuracy of clinically placed pleural aspiration sites have revealed significant potential for visceral injury[15 16] and this is discussed further in the section on image guidance (below).

Image guidance

- **A recent chest radiograph should be available prior to performing a pleural aspiration. (✓)**
- **Thoracic ultrasound guidance is strongly recommended for all pleural procedures for pleural fluid. (B)**
- **The marking of a site using thoracic ultrasound for subsequent remote aspiration or chest drain insertion is not recommended except for large pleural effusions. (C)**

A recent chest x-ray is necessary to confirm the indication for the procedure and the side of the pathology. This should be correlated with the clinical signs. The only exception should be the case of a tension pneumothorax.

Ultrasound-guided pleural aspiration is associated with a lower failure rate and complication rate (see table 1). The procedure failures or 'dry taps' can themselves have further clinically significant complications such as visceral injury.[14] Some studies have shown that pleural aspiration in the hands of experienced operators can achieve low complication rates when conducted without image guidance.[17 18] Table 1 also shows that the use of image guidance can reduce the post-procedure complications even of experienced operators, and a large study of clinical placement of pleural aspiration sites found that inaccurate site placement was independent of operator experience.[15]

There are four studies directly comparing blind pleural aspiration against an ultrasound-guided procedure. In a small randomised controlled trial (n=52) the failure rate (a composite of dry tap and pneumothorax) was 33% with a blind procedure compared with no failures with ultrasound guidance.[19] In a larger retrospective cohort study (n=342)[20] the pneumothorax rate was 18% in the clinically localised pleural aspiration group compared with 3% in the ultrasound-guided group. Within the clinical localisation group were 48 patients with prior ultrasound marking in the radiology department but ward-based pleural aspiration (ie, 'X marks the spot'); subanalysis of this group did not show any difference in the complication rate compared with clinical localisation only. Similarly, Kohan *et al* did not show any difference in complications between clinically sited versus remote ultrasound guidance ('X marks the spot').[21] Another retrospective cohort study (n=523) showed a pneumothorax rate of 10.3% (4.9% requiring a drain) in the blind procedure group compared with 4.9% (0.7% requiring a drain) in the ultrasound-guided group.[22]

A large proportion of these failed blind procedures are probably due to inaccurate clinical site selection. In a study by Diacon *et al*,[15] clinicians were only able to identify a site for a pleural aspiration in 67% of patients with a pleural effusion. In the cohort where a site was identified, 15% were inaccurate and would have resulted in puncture of the lung, liver or spleen. Where the clinician was unable to identify a site for aspiration, ultrasound localised a suitable site for aspiration in 54%. Overall,

Table 1 Complication rates of pleural aspiration by operator and image guidance

Ultrasound guidance	Operator	Frequency of post-procedure pneumothorax	Frequency that a chest drain was required post procedure	Frequency of dry tap/procedure failure
Yes	Radiologist in training	2.7%	1.8%	2.7%
Yes	Senior physician	3.6%	0.9%	3.2%
Yes	Radiologist	2.7%	0.5%	
No	Physician in training	15.0%	4.7%	12.9%
No	Senior physician	5.7%	1.4%	1.6%

The calculations and references used in this table are shown in appendix 1 in the online supplement.[132–134]

ultrasound prevented potential organ puncture in 10% of the procedures and increased the rate of accurate sites by 26%.

Thoracic ultrasound or other imaging is very important following a failed blind pleural aspiration. In a study of 26 patients who had a failed clinically-guided pleural aspiration, 38% had the procedure performed at the incorrect site, 31% had no pleural fluid present, 11% had loculations and 11% had intervening parenchymal consolidation or tumour. Factors associated with failure were a small pleural effusion, loculations and a sharp costophrenic angle on the chest x-ray. Operator inexperience was not associated with failure. Ultrasound-guided pleural aspiration was subsequently successful in 15 of the 17 patients in whom it was attempted.[16] Similarly, Kohan *et al* demonstrated the efficacy of ultrasound-guided pleural aspiration following failed clinical procedures.[21] Therefore, if a clinically localised pleural aspiration fails, image guidance should be performed and no further clinical attempts should be made.

Thoracic ultrasound is also useful in the presence of unilateral 'white-out' or opaque hemithorax on the chest x-ray. In a prospective study of 50 patients, nine had no pleural effusion present on thoracic ultrasound[23] thereby avoiding inappropriate pleural aspiration and potential procedure-related injury.

It could be argued that thoracic ultrasound may not be necessary when aspirating a large pleural effusion that does not cause complete opacification of the hemithorax. In a randomised controlled trial comparing blind pleural aspiration against ultrasound guidance, there was a significantly higher incidence of dry taps in the presence of a small pleural effusion (obliterating less than half of the hemidiaphragm) and loculated pleural effusion. There was no difference in the rate of dry tap in the presence of a large pleural effusion.[21] However, even in this instance, image guidance will reveal underlying abnormalities that are not apparent on plain film radiology such as cardiac enlargement or displacement, a raised diaphragm or adherent lung.

Overall, ultrasound-guided pleural aspiration has been shown to increase the yield and reduce the risk of complications, particularly pneumothoraces and inadvertent organ puncture. However, it should be noted that ultrasound may not reduce the incidence of laceration of the intercostal vessels because they are not visualised on ultrasound.[24] The evidence leads us to conclude that, wherever possible, site selection for all pleural aspiration should be ultrasound-guided. Ultrasound guidance is strongly recommended when attempting to aspirate any pleural effusion. It is even more important when aspirating small or loculated pleural effusions where there is a near or completely radio-opaque hemithorax, particularly in the absence of mediastinum shift away from the side of the lesion or when a clinically-guided attempt has been unsuccessful. However, the use of image guidance does not replace the need for clinical judgement, especially when siting the needle within the intercostal space. The use of ultrasound also requires training and expertise as described later in this document.

Patient position and site of insertion

- **The preferred site for insertion of the needle for pleural aspiration should be the triangle of safety. (✓)**

In determining the correct patient position and site of insertion, it is important for the operator to be aware of the normal anatomy of the thorax and the pathology of the patient. Patient position is dependent on the operator preference and the site of the pathology. In the case of a posterior lying locule, this may be specific to the image-guided spot where fluid is most likely to be obtained. In most circumstances, however, the site of insertion of the needle is either in the triangle of safety (figure 2) or the second intercostal space in the mid-clavicular line. The patient may therefore either sit upright leaning forward with arms elevated but resting on a table or bed, thereby exposing the axilla, or lying on a bed in a position similar to that described in the section on chest drain insertion below.

The needle is inserted in the space just above a rib to avoid damaging the neurovascular bundle. It is common practice to insert the needle more posteriorly for a pleural aspiration, but it should be noted that the neurovascular bundle may not be covered by the lower flange of the rib in this position[25] and a more lateral or anterior site of insertion is considered safer.

Equipment

Pleural aspiration should be aseptic and therefore sterile gloves, a sterile field, skin sterilising fluid and a clean dressing are needed.

For a simple diagnostic pleural aspiration a 21G (green) needle and a 50 ml syringe is sufficient to obtain a sample.

If aspiration of air or a larger sample of fluid is required (therapeutic tap), there are a number of commercially available kits to perform a pleural aspiration although it is often performed in the UK by adapting easily available equipment for the purpose. Most commonly this is an intravenous cannula attached to a three-way tap and tubing/syringe. The tip of the tubing can then be directed into a suitable receptacle for sampling or disposal, or an underwater seal if required.

Aseptic technique

- **Pleural aspiration should take place in a clean area using full aseptic technique. (✓)**

Empyema is a serious and avoidable complication of pleural aspiration, the risk of which is greater with multiple attempts. It is recommended that strict asepsis should be employed, especially when carrying out therapeutic aspirations.

Size of needle

- **Pleural aspiration with large-bore needles should be avoided. (C)**

The use of large-bore needles for pleural aspiration probably increases the risk of developing post-procedure pneumothorax. In addition, if a vascular or visceral injury does inadvertently occur, the use of a large-bore needle is likely to result in more damage than a small-bore needle.

Several studies have linked the use of larger bore needles to an increased rate of post-procedure pneumothorax, although needle

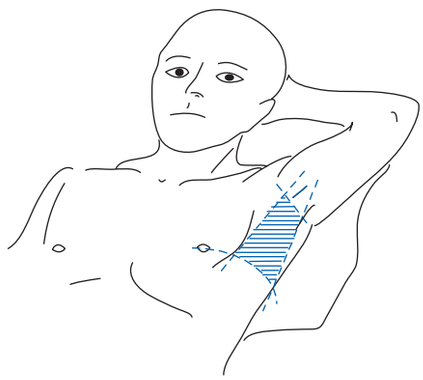

Figure 2 The 'triangle of safety'. The triangle is bordered anteriorly by the lateral edge of pectoralis major, laterally by the lateral edge of latissimus dorsi, inferiorly by the line of the fifth intercostal space and superiorly by the base of the axilla.

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size has not been the prime focus of any study. A large retrospective study and a small prospective study both demonstrated a significantly higher pneumothorax rate after pleural aspirations performed with needle sizes larger than 20G.[19 20] However, a non-randomised prospective study of three different needle types which were different sizes found no difference in the post-procedure pneumothorax rate.[10]

Two other retrospective studies found an increased rate of post-procedure pneumothorax when using larger bore needles. However, both studies were confounded because the larger needles were used to aspirate larger volumes of pleural fluid which itself may increase the rate of complications.[12 26]

The choice of needle length may have to be adjusted in patients with thick thoracic walls. A CT-based study of 53 Scottish patients found that the depth to the pleura was >4.5 cm in the mid-hemithorax line in the second intercostal space in up to 13.2% and up to 47.2% in the mid-axillary line in the fifth intercostal space.[27] This result needs to be interpreted with caution because the tissue thickness in the mid-axillary line will be increased in the supine position owing to soft tissue falling to the side by gravity. Additionally, the soft tissue is often compressible and so a standard needle may be adequate to reach the pleura even if the depth is >4.5 cm on CT imaging. Two studies have measured chest wall thickness on CT scans and found that a standard 40 mm long needle may not be adequate to reach the pleural space in the second intercostal space in some patients. One study was in American military personnel[28] and the other was in a Canadian population.[29]

A reference for needle and chest drain sizes can be found in appendix 2 in the online supplement.

Technique

Thoracic ultrasound should be performed before undertaking pleural aspiration. In the case of a diagnostic pleural aspiration, a syringe attached to a green needle is inserted into the pleural space using the technique described below and 20–50 ml of fluid withdrawn and sent for investigations as discussed in the guideline on investigation of a pleural effusion. Local anaesthesia is not required for a simple procedure but should be considered if difficulty attaining the pleural space is likely (ie, with an inexperienced operator or if the patient has a thick chest wall). Skin cleansing and an aseptic technique should be used.

In the case of a therapeutic aspiration, local anaesthetic should be administered as described in the section on chest drains below. The pleural space should be aspirated with the needle used to administer the local anaesthetic and the depth of the pleural space can then be confirmed. The aspiration needle or cannula should then be advanced into the chest, aspirating continually until the pleura is breached and air or fluid are withdrawn, paying close attention to the depth of the pleural space. The cannula should then be attached to a three-way tap and fluid/air withdrawn into the syringe and expelled via the free port of the three-way tap. This may be into a bag or jug for fluid, or into air or a tube inserted into a bottle under water acting as a one-way seal to prevent air being entrained.

This process should be repeated and continued until the procedure is terminated. The cannula is then removed and a simple dressing applied.

Volume of removal, re-expansion pulmonary oedema and the use of pleural manometry

- **The procedure should be stopped when no more fluid or air can be aspirated, the patient develops symptoms of cough or chest discomfort or 1.5 l has been withdrawn. (C)**

The maximum volume which can be aspirated is subject to debate as there is concern that re-expansion pulmonary oedema (RPO) may occur and that the frequency of post-procedure pneumothorax may increase if larger volumes of fluid are withdrawn.

The rate of RPO has been quoted as being anywhere between 0.2% and 14%. In more recent studies[30–32] the incidence of clinical RPO is <1% but asymptomatic radiologically-apparent RPO may be slightly more frequent. It is unlikely to occur if <1 l is withdrawn, but it is less clear how cases at risk of RPO can be predicted at higher volumes.

The amount of fluid which may be safely removed at one time continues to be debated and in many studies up to 3 l has been safely aspirated. Aspiration of up to 6.5 l[30] without complication has been described. Advice has generally been conservative because of the morbidity associated with RPO and a mortality rate quoted as high as 20%.[33]

In a retrospective study of 735 pleural aspirations, Josephson *et al* found that draining 1.8–2.2 l was associated with a three-fold increase in the frequency of post-procedure pneumothoraces compared with draining 0.8–1.2 l. They also found that draining >2.3 l was associated with an almost sixfold increase, although this subset only consisted of 21 procedures.[34] Similar findings were made in other retrospective studies,[12 20 26] although another failed to show any difference.[10]

It is possible that the association between the volume of fluid drained and the increase in occurrence of post-procedure pneumothorax is due in part to underlying trapped lung. If a greater volume of fluid is drained, then an underlying trapped lung is more likely to be revealed. This mechanism of post-aspiration pneumothorax has been discussed previously in the section on complications.

Although the safe aspiration of much larger volumes has been documented, it is also clear that complications are uncommon when aspirating <1.5 l. This is therefore the recommended volume to be aspirated at one attempt.

If symptomatic RPO does occur, the mainstay of management should be close cardiovascular and respiratory monitoring and oxygen therapy which is sufficient in many cases.[35 36] Continuous positive airways pressure (CPAP) has been used in a number of cases with success.[37 38] If using CPAP, caution should be taken to avoid recurrent pneumothorax and potential tension pneumothorax if the RPO has occurred following the aspiration of a pneumothorax and there is no pleural drain in place. The use of diuretics[30 39] and steroids[39] have also been described, although there is little evidence to support it and some authors counsel against their use.[36]

Pleural manometry is a technique whereby the pleural pressure is measured by connecting a water-filled manometer or an electric transducer to the thoracocentesis catheter via a three-way tap. This enables the initial pleural pressure to be measured and at intervals throughout the thoracentesis. While the initial pressure does not predict the pathology of the fluid, the pressure is most negative in cases of trapped lung. It is proposed in the papers describing this procedure that thoracentesis should be terminated when the pleural pressure falls to less than −20 cm H_2O as this could predict the risk of RPO, the value being based on animal models. While there have been no randomised controlled trials to confirm this, in the cases series described there were no cases of RPO by using this method with >6 l of fluid being removed.[40]

Pleural manometry is not currently in clinical practice in the UK, there are no comparative studies and there is no commercially-designed equipment specific for this procedure.

Follow-up

- **A chest x-ray after a simple pleural aspiration is not required unless air is withdrawn, the procedure is difficult, multiple attempts are required or the patient becomes symptomatic. (C)**

It is current practice to request a chest x-ray after pleural aspiration to exclude a pneumothorax. In a study of 278 cases of pleural aspiration Petersen *et al* assessed the ability of physicians to detect significant post-aspiration pneumothoraces. Of the 15 patients in whom the physician suspected a post-procedure pneumothorax, nine were subsequently found to have a pneumothorax. In all nine, air was freely aspirated at the time of the procedure. Only 2.3–3.3% of the cases in which no pneumothorax was suspected were subsequently found to have one, and all of these cases used a vacuum bottle to aspirate the pleural effusion.[41] Another study[9] showed that, in 174 pleural aspirations, five out of eight of the pneumothoraces that occurred were expected and none of the unsuspected cases required intervention. Two of the five cases with pneumothorax had had multiple procedures.[9] Capizzi *et al* found that pneumothorax was present in five of 54 chest x-rays performed after pleural aspiration for fluid as outpatients and no symptomatic complications were found in a further 50 cases who did not have a chest x-ray.[42]

We conclude that the physician performing an aspiration can usually predict the presence or absence of a clinically significant post-procedure pneumothorax and therefore a post-aspiration chest x-ray is not routinely needed. The use of vacuum bottles during aspiration can hinder the operator's ability to detect inadvertently aspirated air.

INSERTION OF CHEST DRAINS

A chest drain is a tube which is placed in the pleural space to drain its contents (fluid or air) and remains in place until drainage is complete.

Indications

The indications for chest drain insertion are shown in box 2.

Consent

- **Written consent should be obtained for chest drain insertions, except in emergency situations.**

The General Medical Council (GMC) guideline[43] *'Consent: Patients and Doctors Making Decisions Together'* states that it is the responsibility of the doctor carrying out a procedure or an appropriately trained individual with sufficient knowledge of a procedure to explain its nature and the risks associated with it in a language which is understandable to the patient. It is within the rights of a competent individual patient to refuse such treatment, and patients without mental capacity should be treated following the appropriate advice given in the GMC guidance. As insertion of a chest drain is a procedure associated with significant risk, consent should be obtained in writing and should include the commonest and most serious complications as outlined below and also the possibility of treatment failure. In the case of an emergency when the patient is unconscious and the treatment is lifesaving, treatment may be carried out but must be explained as soon as the patient is sufficiently recovered to understand. An information leaflet should be given where available prior to the procedure (see appendix 3 in online supplement).

Box 2 Indications for chest drain insertion

Pneumothorax*
- In any ventilated patient
- Tension pneumothorax after initial needle relief
- Persistent or recurrent pneumothorax after simple aspiration
- Large secondary spontaneous pneumothorax in patients aged >50 years

Malignant pleural effusions ± pleurodesis*
Empyema and complicated parapneumonic pleural effusion*
Traumatic haemopneumothorax
Post-surgical (eg, thoracotomy, oesophagectomy, cardiac surgery)

* Refer to specific guidelines for further detail.

Complications

- **Pain, intrapleural infection, wound infection, drain dislodgement and drain blockage are the most frequent complications of small-bore chest drain insertion. Visceral injury is the most serious complication. All of these possible sequelae should be detailed in the consent process. (✓)**
- **Pain, intrapleural infection, wound infection, drain-related visceral injury and drain blockage are the most frequent complications of large-bore chest drain insertion. All of these possible sequelae should be detailed in the consent process. (✓)**

Numerous case reports have described a range of serious complications associated with chest drains including visceral puncture and serious bleeding, which fortunately are rare. There are also reports of nerve damage to both the intercostal nerves during insertion and nerve bundles within the thoracic cavity from the drain itself (Horner's syndrome being one of the more commonly recorded), but these also seem to be sporadic cases. A survey of UK NHS Trusts found that the majority of them had experienced a major complication following a chest drain insertion between 2003 and 2008. There were 17 fatalities reported during this time which were mainly due to misplaced drains.[2] Complications have been reported to be highest in large-bore chest drains inserted in trauma patients using the trocar technique. The lowest reported complication rates are seen in studies where small drains are inserted by consultant radiologists. It is likely that complications are reduced by using ultrasound guidance and this has been recommended by the NPSA.[1]

The most commonly occurring complications in the studies examined are shown in tables 2 and 3. Pneumothorax is also commonly reported, but the aetiology is multifactorial ranging from lung injury and introduction of air to 'trapped lung', which is not regarded as a procedural complication (see section on pleural aspiration). Simple pneumothoraces are easily dealt with by the chest drain itself and, where possible, we have reported lung injury under the 'injury' column in tables 2 and 3.

Table 2 Frequency of post-insertion complications for small drains (≤16 F)

Complication	Total no.*	Calculated frequency	Range	Studies
Injury	582	0.2%	0–2%	44–51
Malposition	593	0.6%	0–9%	45–52
Empyema	395	0.2%	0–2%	45, 48–51
Drain blockage	341	8.1%	2–18%	45, 48–52

*Total number of procedures performed from the studies found that quote this complication.

Table 3 Frequency of post-insertion complications for large-bore drains (≥20 F or stated 'large-bore drain')

Complication	Total no.*	Calculated frequency	Range	Studies
Injury	1572	1.4%	0–7.9%	44, 52–60
Malposition	1778	6.5%	1.1–31%	53–61
Empyema	1778	1.4%	0–2%	53–61
Drain blockage	115	5.2%	5.2%	52

*Total number of procedures performed from the studies found that quote this complication.

Liu *et al*[44] studied pneumothorax treatment and reported three cases of haemothorax as a complication; these are also reported in the 'injury' column.

Tables 2 and 3 are separated into small-bore drains and large-bore drains for ease of reference, although they cannot be directly compared owing to significant differences in the insertion technique, the use of image guidance and the indications for the drains to be inserted. These differences are described in more detail in the table in appendix 4 in the online supplement. There is also a range of operator experience in the studies with a tendency for small-bore image-guided drains to be inserted by more senior operators; these factors are likely to explain the different malposition rates for the two types of drain.

Antibiotic prophylaxis

- **Antibiotic prophylaxis is not recommended for non-trauma patients requiring a chest drain. (✓)**
- **Antibiotic prophylaxis should be considered for trauma patients requiring chest drains, especially after penetrating trauma. (A)**

The rate of empyema and wound infection in trauma cases has been reported to be as high as 5.8–13%. A number of studies,[62–68] including a meta-analysis[69 70] of 507 cases of thoracic trauma requiring chest drainage comparing empirical antibiotics with placebo, showed an absolute reduction in infection and empyema in the treatment group of 5.5% (OR 5.27 in favour of giving antibiotics). It should be noted, however, that these studies were of different types of thoracic trauma (blunt and penetrating) and occurred in predominantly young male patients in a variety of settings. In addition, the environment in which the chest drain was inserted may not have been fully aseptic in some cases. The antibiotics used have varied from study to study, but all have shown a reduction in the infection rates. The studies are summarised in the evidence table which is available on the BTS website at www.brit-thoracic.org.uk.

The use of antibiotic prophylaxis in medically inserted chest drains has not been studied but, given the low rates of infection and the risk of hospital-acquired infections such as *Clostridium difficile* and the older age group of these patients, it cannot be recommended at this time.

Equipment

The equipment required is shown in box 3.

Size of drain

- **Small drains should be used as first-line therapy for pneumothorax, free flowing pleural effusions and pleural infection. (C)**

Traditionally, large-bore drains were recommended and inserted using a blunt dissection technique. With the increased availability of small drains and use of the Seldinger technique this has now become the most common mode of chest drain insertion, such that many trainee doctors are not able to insert large-bore drains except emergency doctors or surgeons who have undergone ATLS training.

Box 3 Equipment

- Sterile gloves and gown
- Skin antiseptic solution (eg, iodine or chlorhexidine in alcohol)
- Sterile drapes
- Gauze swabs
- A selection of syringes and needles (21–25 gauge)
- Local anaesthetic (eg, lidocaine 1%)
- Scalpel and blade
- Suture (eg, 0 or 1-0 silk)
- Instrument for blunt dissection if required (eg, curved clamp)
- Guide wire and dilators for Seldinger technique
- Chest tube
- Connecting tubing
- Closed drainage system (including sterile water if underwater seal being used)
- Dressing

Equipment may also be available in kit form.

Small-bore chest drains have a low risk of serious complications, as demonstrated in table 2. Small-bore catheters have significantly lower pain scores and analgesia requirements and a greater degree of comfort than in comparable patients in whom large-bore catheters have been inserted for the same indication.[71 72] Davies *et al* described high overall complication rates (42%) with small-bore drains, but the majority of these were dislodgement (21%), blockage (9%) or pain (5%).[51] Collop *et al* also described a higher complication rate with small-bore drains (36%) than with large-bore drains (9%). In this study, however, the small-bore drain group was substantially smaller (11 patients vs 115 patients) and the complications were less severe (malposition, blockage and kinking in the small-bore drain group versus one episode of possible lung laceration and a site infection as well as others in the large-bore drain group).[52]

The relatively low risk of complications with small-bore drains inserted using the Seldinger technique is generally accepted, but there is greater debate regarding the effectiveness of small-bore drains in various clinical situations.

One of the arguments put forward for using larger drains is the greater flow that is possible as predicted by Poiseuille's law. However, the maximum rate of drainage possible through a drain is unlikely to be important when draining a pleural effusion when the rate of flow is usually deliberately controlled.

Rate of flow may theoretically be more of an issue when draining pneumothoraces with a persistent high volume air leak. This theoretical advantage is not borne out in the majority of clinical cases of pneumothorax where the use of smaller drains (≤14 F)[44–46 48 50 73] had similar rates of success for draining pneumothoraces as the larger drains.[44 45 61] Liu *et al* compared conventional chest tubes with small bore (8–10 F) drains for the management of spontaneous pneumothorax in a retrospective review of a change in their practice and found the success rates to be comparable. Of the 15 patients in their small-bore drain group who needed further management, all went on to receive a conventional chest tube; 4 (27%) resolved with this management and 11 (73%) subsequently needed surgery.[44] Other small retrospective studies comparing large and small drains have shown them to be equivalent in the acute management of primary spontaneous pneumothorax. One suggested that there

is a higher rate of recurrence associated with the use of small-bore drains,[74] although this has not been borne out in other studies.[44 75]

Small-bore chest drains inserted by the Seldinger technique are therefore recommended as first-line therapy for spontaneous pneumothoraces and iatrogenic pneumothoraces; however, a larger bore drain may be needed in cases of very large air leaks, especially postoperatively.

Drainage of simple pleural effusions is also effectively done with a small-bore drain.[45–49 61] It is likely that the limiting factor when using a small-bore chest drain is the connecting of a two- or three-way tap as this has a narrower bore than the drain.[76]

Parulekar *et al* and Clementsen *et al* compared small-bore and large-bore drains when draining malignant pleural effusions and performing sclerotherapy.[71 77] They found no difference between the two groups with regard to time taken to drain the effusion prior to sclerotherapy or the effectiveness of the sclerotherapy. Clementsen *et al* also showed that the small-bore drain group found the experience of drain insertion and the presence of the drain a less unpleasant experience than those in the large-bore drain group.[71]

We recommend that small-bore drains are the first choice for draining pleural effusions.

The use of small-bore drains to drain empyemas has a very variable success rate across studies.[45–47 78–81] The most common problem is drain blockage [45 46] and drain dislodgement.[51] It is likely that the limiting factor when using a small-bore chest drain is the connecting of a two- or three-way tap as this often has a narrower bore than the drain.[76] Davies *et al* suggest that regular flushing reduces the rate of drain blockage[51] and studies that employed regular flushing of the drains with either saline or a fibrinolytic drug have higher therapeutic success rates.[78–81]

We therefore recommend that image-guided small-bore drains should be used as first-line therapy for the treatment of empyema. Regular flushing is probably helpful but needs further investigation. More than one drain may be needed to achieve successful drainage. Subsequent drains may be necessary to drain separate loculations or to replace drains that have become blocked.[46 79 80]

Large-bore drains may be helpful if small-bore drainage fails but, equally, image-guided small-bore drainage can be therapeutically successful when large-bore drainage fails.[80 82 83]

Analgesia and sedation

- **To reduce pain associated with chest drains, analgesia should be considered as premedication and should be prescribed for all patients with a chest drain in place. (✓)**
- **If formal sedation is used during the procedure, this should be given in line with the recommendation of the Academy of Royal Colleges for conscious sedation and include oximetry recording throughout the procedure. (✓)**

Chest drain insertion has been reported to be a painful procedure with 50% of patients experiencing pain levels of 9–10 on a scale of 10 in one study[4] and therefore premedication should be considered. Despite the apparent common sense of this approach, there is little established evidence of the effect from these medications and there are concerns for the safety of this approach in operators unfamiliar with safe sedation techniques. The Royal College of Anaesthetists in association with the Academy of Royal Colleges issued guidance for conscious sedation, and doctors should be familiar with these guidelines before employing this technique.[84]

Premedication could be with an intravenous anxiolytic (eg, midazolam 1–2 mg titrated to achieve adequate sedation) or an analgesic (eg, 2.5 mg intravenous morphine given immediately prior to the procedure or 10 mg oromorph 1 h prior to the procedure). No single technique has been shown to be clearly superior. Both these classes of drugs may cause respiratory depression and all patients who receive them should be observed. Patients with chronic obstructive pulmonary disease are particularly at risk and require extra care when using these drugs. Reversal agents (eg, naloxone or flumazenil) are occasionally necessary and should always be immediately accessible if using intravenous opiates or benzodiazepines. Intravenous access should be maintained throughout the procedure and oxygen saturation should be monitored continuously. Sedation should allow the patient to remain conversant throughout the procedure and should be combined with a sensitive explanation during the procedure with reassurance.

While the use of atropine as part of premedication for fibreoptic bronchoscopy has been assessed, no controlled trials of its use in chest tube insertion were found although it is advocated in some centres. Case reports of vasovagal reactions and a death due to vagal stimulation following tube insertion may support its use as premedication.

Patient position and site of insertion

The preferred position for standard drain insertion is on the bed, slightly rotated, with the arm on the side of the lesion behind the patient's head (figure 3A) or on the hips to expose the axillary area or in the lateral decubitus position (figure 3C). An alternative is for the patient to sit upright leaning over an adjacent table with a pillow under the arms (figure 3B).

Insertion should be in the 'triangle of safety' illustrated in figure 2. This is the area bordered by the lateral edge of the latissimus dorsi, the lateral border of the pectoralis major muscle

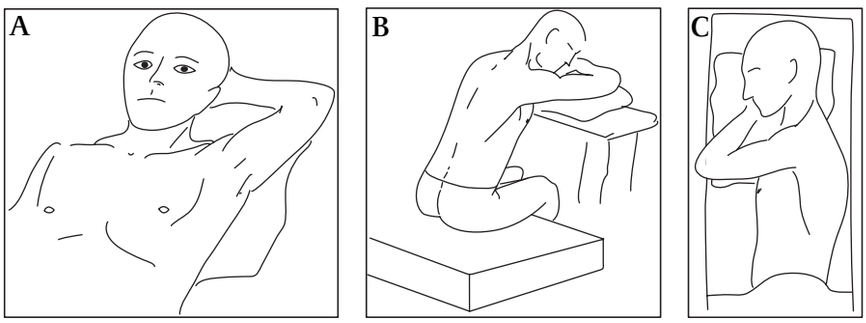

Figure 3 Common patient positions for chest drain insertion. (A) Semi-reclined with hand behind head. (B) Sitting up leaning over a table with padding. (C) Lateral decubitus position.

and superior to the horizontal level of the fifth intercostal space. This position minimises the risk to underlying structures (eg, internal mammary artery) and avoids damage to muscle and breast tissue resulting in unsightly scarring.

For apical pneumothoraces the second intercostal space in the mid-clavicular line is sometimes chosen but is not recommended routinely. This position may be uncomfortable for the patient and is more visible if the drain insertion leaves an unsightly scar. It may be the preferred site when using a small drain with an ambulatory drainage system. Loculated apical pneumothoraces are not uncommonly seen following thoracotomy and may be drained using a posteriorly (suprascapular)-sited apical tube. This technique should, however, be performed under image guidance or by an operator experienced in this technique such as a thoracic surgeon. If the drain is to be inserted into a loculated pleural collection, the position of insertion will be dictated by the site of the locule as determined by imaging.

Confirming site of insertion

- **During chest drain insertion an attempt to aspirate the pleural contents with a small needle should be made. If this is not possible, chest drain insertion should not continue. (✓)**

Immediately before the procedure the identity of the patient should be checked and the site and side for insertion of the chest tube confirmed by reviewing the clinical signs and the chest x-ray. Once a safe site for chest drain insertion has been identified and prior to the insertion of a drain, the expected pleural contents (air or fluid) should be aspirated with a small needle, usually while administering local anaesthesia. If none is forthcoming, further imaging is required.

Image guidance

- **It is strongly recommended that all chest drains for fluid should be inserted under image guidance. (B)**

There is less evidence comparing ultrasound guidance against clinical guidance for chest drain insertion than there is for pleural aspiration. Intuitively, the use of thoracic ultrasound should reduce the risk of drain malposition and complications as the data regarding accuracy of site selection, as described in the pleural aspiration section, is as relevant for chest drain insertion as it is for pleural aspiration.

Several studies have successfully used ultrasound-guided small-bore chest drains in the treatment of pneumothorax,[46 73] pleural infection[46 47 78–80] and pleural effusion[46 47] with high levels of efficacy and low complication rates. However, it is difficult to determine the exact contribution of ultrasound as these studies often used mixed modality imaging including CT and fluoroscopy.

Ultrasound is useful in guiding the insertion of a chest drain into free-flowing pleural effusions. Keeling[47] demonstrated that, in a subgroup of 30 patients, image-guided chest drains were 100% successful in treating simple non-infected pleural effusions. The majority of drains were inserted using ultrasound guidance. However, in one patient the chest drain was incorrectly sited within the subcutaneous tissue and was correctly re-sited using CT guidance. There were no serious complications.

Several studies have shown that image-guided small drains are effective in the management of pleural infections, particularly when the effusions are loculated. No studies were found that directly compared image-guided drainage with other methods of treatment such as non-image guided small-bore or large-bore drainage. Moulton *et al*,[79] Keeling *et al*,[47] Cantin *et al*,[85] Silverman *et al*[80] and Akhan *et al*[78] have all used ultrasound guidance to direct small-bore drains for the treatment of pleural infection with a success rate of 73–94%. Ultrasound can be used to direct chest drains into the largest loculation or into two or more separate collections when treating multiloculated effusions with good effect. CT should be used if the abnormalities are poorly visualised on ultrasound.[80] Van Sonnenberg *et al*[83] used the greater positional accuracy of image-guided small-bore catheters to successfully treat patients with empyema who had failed management with conventional chest tube drainage. Of the 17 catheters included in the study, 13 were inserted following failure of standard chest tube therapy (of these, 10 were in the wrong position and 2 were in small locules). Overall, image-guided small-bore drains were successful in 13 of the cases (76.5%).

Thoracic ultrasound is of limited utility in guiding insertion of a chest drain in the presence of a pneumothorax because of the difficulty in obtaining useful images due to the poor transmission of sound waves through air.

Aseptic technique

- **Chest drains should be inserted in a clean area using full aseptic technique including gowns, drapes, sterile gloves and skin cleansing. (C)**

Although this is uncommon, estimations of the empyema rate following drain insertions are approximately 0.2–2.4% (tables 2 and 3) for medically inserted chest drains in formal studies but may be higher in routine practice. This may be because, in published studies looking at complication rates, the drains were inserted in dedicated areas in emergency rooms or theatres with full aseptic technique being employed.

Infection following chest drain insertion, both cutaneously and within the pleural space, is an avoidable complication of the procedure and we therefore recommend that full aseptic technique including sterile gloves, drapes and gowns is used.

We also recommend that chest drains are inserted in a clean area away from sources of contamination and with enough space so that the sterile field can be preserved. This should be separate from a general ward area.

Local anaesthesia

- **Lidocaine 1% should be infiltrated prior to the procedure, paying particular attention to the skin, periostium and the pleura. (✓)**

Chest drain insertion is described as a very painful procedure by patients and can be improved by better training, use of sedation (see above) and liberal use of local anaesthesia. In centres which undertake medical thoracoscopy, it is recognised that this can be a relatively painless procedure and it is therefore likely that a similar technique applied to chest drain insertion will be successful although there is no evidence to confirm this.

Expert opinion is that local anaesthetic is infiltrated into the site of insertion of the drain. A small-gauge needle is used to raise a dermal bleb before deeper infiltration of the intercostal muscles and pleural surface. As the skin, the pleura and periostium are the most sensitive areas, this is where most of the anaesthesia should be infiltrated. A spinal needle may be required in the presence of a thick chest wall, but image guidance is strongly recommended if the pleura cannot be breached by a green needle to ensure localisation of the correct site.

Local anaesthetic such as lidocaine (up to 3 mg/kg) is usually infiltrated. Higher doses may result in toxic levels. The peak concentration of lidocaine was found to be <3 μg/ml (ie, low risk of neurotoxic effects) in 85% of patients given 3 mg/kg intrapleural lidocaine. The volume given is considered to be more

important than the dose to aid spread of the effective anaesthetic area and therefore a dilute preparation (1% rather than 2%) is preferable. The use of epinephrine to aid haemostasis and localise the anaesthesia is used in some centres but has not been studied in this context. The use of epinephrine allows up to 5 mg/kg lidocaine to be infiltrated.

Insertion technique

- **Drains should never be inserted using substantial force. (✓)**
- **The dilator should not be inserted further than 1 cm beyond the depth from the skin to the pleural space. (✓)**
- **Blunt dissection should be employed in cases of trauma or insertion of large-bore drains. (C)**

Small-bore Seldinger technique

The Seldinger technique to insert a chest tube has become the most widespread method of drain insertion since the publication of the previous guidelines in 2003. In many centres it is the only method of drain insertion on medical wards and many doctors have never been trained to insert a drain any other way. When this technique was introduced it was thought it would be an easier and safer way to insert a drain based mainly on the initial experience by radiologists inserting under ultrasound guidance. The technique can be carried out safely by other doctors as long as they are appropriately trained and familiar with the equipment used in their hospital.

A needle is introduced into the pleural space and the pleural contents should be aspirated at this stage to confirm the position of the needle tip in the pleural space. The depth of the needle when it enters the pleural space is noted. A guide wire is passed through the needle which can be used to gently guide the wire to the apex or the base of the pleural cavity as required. The needle is then withdrawn leaving the guide wire in place and a small skin incision is made. The dilator is then passed gently over the guide wire using a slight twisting action. Many of the reported injuries as a result of chest drain insertion were due to visceral puncture by the dilator. Force is unnecessary and the dilator only needs to be passed 1 cm beyond the depth to the pleura as measured with the introducer needle. By holding the dilator firmly at this depth or using a marker available with some kits, excessive insertion depth can be avoided.

The tract is further widened by using a series of enlarging dilators up to the size of the drain. The drain is then inserted gently over the wire aiming upwards for pneumothorax or as appropriate for the fluid to be drained. The depth should be enough to ensure the last drainage hole is well within the pleural space (approximately 5–10 cm) but does not require insertion to the hilt. The guide wire is then removed leaving the drain in place. The drain should be stoppered until secured and then connected to a drainage system.

Large-bore blunt dissection

- **Surgically inserted chest drains should be inserted by blunt dissection. Trocars should not be used. (C)**

Once the anaesthetic has taken effect, an incision is made just above and parallel to a rib. This should be slightly bigger than the operator's finger and tube.

Many cases of damage to essential intrathoracic structures have been described following the use of trocars to insert large-bore chest tubes. The use of a trocar to guide a chest drain insertion is associated with the highest complication rates[58] and, in a recent study of malpositioned chest tubes, all had been inserted by the trocar technique.[86] A trocar should therefore never be used.

Blunt dissection of the subcutaneous tissue and muscle into the pleural cavity has therefore become universal and is essential. In one retrospective study[87] only four technical complications were seen in 447 cases using blunt dissection. Using a Spencer–Wells clamp or similar, a path is made through the chest wall by opening the clamp to separate the muscle fibres. For a large chest drain (>24 F), this track should be explored with a finger through into the thoracic cavity to ensure there are no underlying organs that might then be damaged at tube insertion. This is essential in the case of thoracic trauma where displacement of internal organs may make insertion of the drain particularly hazardous. Excessive force should never be required during drain insertion.

Sutures and securing the drain

A common complication of drain insertion is accidental removal of the drain, usually as a result of inadequate securing techniques.

The drain itself should be secured after insertion to prevent it falling out. Various techniques have been described but a simple technique of anchoring the tube has not been the subject of a controlled trial. The chosen suture should be stout and non-absorbable (eg,'0' or '1-0' silk) to prevent breaking and it should include adequate skin and subcutaneous tissue to ensure it is secure. Commercially available dressings may also be used which fix to the skin and then attach to the drain. It should be emphasised that, while these dressings are useful for stabilising the drain at the skin and preventing kinking at the skin surface, they do not replace the need to stitch the drain firmly in place.

Large amounts of tape and padding to dress the site are unnecessary and concerns have been expressed that they may restrict chest wall movement or increase moisture collection. A transparent dressing allows the wound site to be inspected by nursing staff for leakage or infection. An omental tag of tape has been described which allows the tube to lie a little away from the chest wall to prevent tube kinking and tension at the insertion site (figure 4).

In the case of a large-bore drain, a suture for wound closure should be placed at the time of the drain insertion. A 'mattress' suture or sutures across the incision are usually employed and, whatever closure is used, the stitch must be of a type that is appropriate for a linear incision. Complicated 'purse-string' sutures must not be used as they convert a linear wound into a circular one that is painful for the patient and may leave an

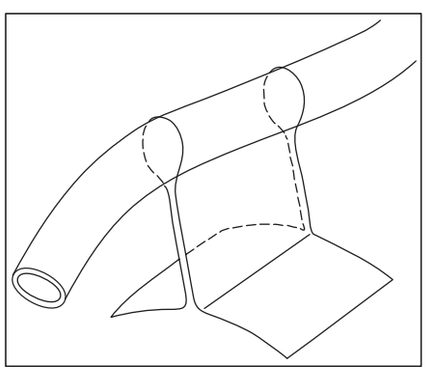

Figure 4 The omental tape technique.

unsightly scar. A suture to close the wound is not usually required for small-gauge chest tubes.

Drain position

- **If malposition of a chest drain is suspected a CT scan is the best method to exclude or confirm its presence. (C)**
- **A chest drain may be withdrawn to correct a malposition but should never be pushed further in due to the risk of infection. (✓)**
- **A further drain should never be inserted through the same hole as a previously dislodged drain as this can introduce infection. (✓)**

If possible, the tip of the tube should be aimed apically to drain air and basally for fluid. However, successful drainage can still be achieved when the drain is not placed in an ideal position and therefore effectively functioning tubes should not be repositioned simply because of a suboptimal radiographic appearance.

In the case of a drain which fails despite an apparent acceptable position on the plain chest x-ray, a CT scan may be performed and demonstrate the cause. A chest tube may be intraparenchymal or extrapleural and the chest x-ray may give no indication of its malposition.[55 56 88]

Drainage systems

- **A chest drain should be connected to a drainage system that contains a valve mechanism to prevent fluid or air from entering the pleural cavity. This may be an underwater seal, flutter valve or other recognised mechanism. (✓)**

A number of drainage systems are available. The most common is the underwater seal bottle although flutter bags and Heimlich valves have been successfully used to achieve ambulatory drainage and numerous other examples have been described. All drainage systems allow only one direction of flow.

The closed underwater seal bottle is a system in which a tube is placed under water at a depth of approximately 3 cm with a side vent with allows escape of air or may be connected to a suction pump. This enables the operator to see air bubble out as the lung re-expands in the case of pneumothorax or fluid evacuation rate in empyemas, pleural effusions or haemothorax. The continuation of bubbling suggests a continued visceral pleural air leak, although it may also occur in patients on suction when the drain is partly out of the thorax and one of the tube holes is open to the air. The inspiratory swing in the tube is useful for assessing tube patency and confirms the position of the tube in the pleural cavity. The disadvantages of the underwater seal system include the obligatory inpatient management, difficulty of patient mobilisation and the risk of knocking the bottle over.

The use of integral Heimlich flutter valves has been advocated in the case of pneumothoraces, especially as they permit ambulatory or even outpatient management which has been associated with a success rate of 85–95%. In 176 cases of pneumothorax treated with small chest tubes and a Heimlich flutter valve there were only eight failures (hospital admissions for problems with tube function or placement).[89] The average length of inpatient stay has been quoted as 5 h with a thoracic vent and 144 h with an underwater seal, with a cost saving of US$5660.[90] Case reports of incorrect use (wrong direction of flow) of such valves have been described, however, with tension pneumothorax as a result. Flutter valves cannot be used with fluid drainage as they tend to become blocked. However, in the UK a similar short hospital stay is achieved by initial aspiration of pneumothoraces (see pneumothorax guidelines).

The use of a drainage bag with an incorporated flutter valve and vented outlet has been successfully used postoperatively but has also been used successfully in clinical practice. In the case of malignant pleural effusion drainage, a closed system using a drainage bag or aspiration via a three-way tap has been described to aid palliation and outpatient management. The more recent development of indwelling tunnelled pleural catheters is likely to replace this.

Management of a chest drain

- **All patients with chest drains should be cared for by a medical or surgical team experienced with their management and nursed on a ward familiar with their care. (✓)**

Rate of fluid drainage and clamping the drain

- **A bubbling chest tube should never be clamped. (C)**
- **A maximum of 1.5 l should be drained in the first hour after insertion of the drain. (C)**
- **Drainage of a large pleural effusion should be controlled to prevent the potential complication of re-expansion pulmonary oedema. (C)**

Clamping a chest drain in the presence of a continuing air leak may occasionally lead to the potentially fatal complication of a tension pneumothorax. A bubbling drain should therefore never be clamped.

It is felt that a general rule not to clamp a drain is the safe approach in most instances to avoid clamping being carried out inappropriately by less experienced clinicians. However, many experienced physicians support the use of clamping of chest drains prior to their removal to detect small air leaks not immediately obvious at the bedside. By clamping the chest drain for several hours followed by a chest x-ray, a recurrence of a pneumothorax may be ruled out. Such a strategy, though not generally recommended, may be acceptable for experienced specialists. The clamped drain should be closely supervised by nursing staff who are familiar with the management of chest drains and who should unclamp the chest drain in the event of any clinical deterioration.

In the case of pleural effusions, the volume of fluid drained in the first hour should be a maximum of 1.5 l. After an hour the rest of the fluid may be drained off slowly. The fluid volume should be controlled in this fashion to avoid the risk of RPO (see earlier).

Suction

There is no evidence to recommend or discourage the use of suction in a medical scenario, however it is common practice especially in the treatment of non-resolving pneumothoraces. In trauma and postoperative patients, suction has been shown not to improve pneumothorax resolution times or chest drain duration[91 92] and, in some cases, may potentially be detrimental.[93 94] It is difficult, however, to extrapolate this evidence to the medical use of chest drains. One study did include patients with spontaneous pneumothorax and again found that the use of suction did not alter treatment outcome, but the number of patients was small.[95]

If suction is required, this may be done by the underwater seal at a level of 10–20 cm H_2O. A high-volume low-pressure system (eg, Vernon-Thompson) is required to cope with a large leak. A low-volume high-pressure pump (eg, Roberts pump) is inappropriate as it is unable to cope with the rapid flow, thereby effecting a situation similar to clamping and risking formation of a tension pneumothorax. A wall suction adaptor may also be

effective, although chest drains must be connected to a specialised thoracic suction regulator and not directly to the high negative pressure regulators that are used for other purposes.

Nursing care of a chest drain

- **Chest drains should be managed on wards familiar with chest drains and their management. (✓)**
- **Drains should be checked daily for wound infection, fluid drainage volumes and documentation for swinging and/or bubbling. (✓)**

Patients should be managed on a ward familiar with chest tubes. The appropriate training of the nursing staff is imperative and communication between the medical and nursing staff regarding the chest drain care is vital. If an underwater seal is used, instructions must be given to keep the bottle below the insertion site at all times, to ensure that it is kept upright and that there is adequate water in the system to cover the end of the tube. Daily reassessment of the amount of drainage/bubbling and the presence of respiratory swing should be documented preferably on a dedicated chest drain chart. Instructions with regard to chest drain clamping must be given and recorded.

Patients should be encouraged to take responsibility for their chest tube and drainage system. They should be taught to keep the underwater seal bottle below the level of their chest and to report any problems such as pulling on the drain insertion site. Educational material (eg, leaflets) should be available on the ward for patients and nursing staff.

Removal of drain

The chest tube should be removed once the fluid drainage has decreased to less than 200 ml per day, resolution of the pneumothorax (see specific guidelines) or when the drain is no longer functioning. Removal is with a brisk firm movement while an assistant ties the previously placed mattress suture. In a study comparing removal in inspiration or expiration with a Valsalva manoeuvre, there was no difference in the immediate or short-term rate of pneumothorax.[96]

In the case of pneumothorax, the drain should not usually be removed until bubbling has ceased in the presence of evidence of tube patency and chest x-ray demonstration of re-inflation. Clamping of the drain prior to removal is generally unnecessary. When considering removal of a drain under suction, in trauma patients, a period of water seal only drainage prior to removal probably reduces the rate of recurrence of significant pneumothorax after removal[97] although the results of a smaller study dispute this.[98] There are no studies to guide medical practice, although it is common practice to allow a period of water seal only drainage after suction and before the drain is removed to check that a pneumothorax does not recur off suction.

THORACIC ULTRASOUND

Ultrasound physics

Medical ultrasound uses sound waves between 2.5 and 12 MHz generated by a transducer to interrogate tissue. The sound waves are attenuated as they travel through tissue. Some or all of these waves are reflected at the interface between tissues where a difference between tissue impedance exists. The returning waves are detected by the transducer and converted into an image.

An understanding of the physical laws governing the transmission of sound waves in solids and fluids will facilitate an understanding of the acquired image and optimisation of the scanning technique.

Fluid is an excellent conductor of sound waves and appears black on ultrasound whereas air effectively blocks all transmission of sound waves and generates a random snowstorm image. Internal organs such as the liver or spleen have variable echogenicity depending on the proportion of sound waves reflected by the structure.

The maximal depth and resolution of an ultrasound image is related to the frequency of the sound waves. Lower frequencies have longer wavelengths and hence better tissue penetration but lower resolution. Higher frequencies have shorter wavelengths which provide higher resolution images and at a greater refresh rate but poor tissue penetration.

Normal thoracic ultrasound appearance

Ultrasound examination of the thorax is limited by air within the lungs, which is a poor conductor of sound waves, and the acoustic shadow caused by the bony structures surrounding the thorax such as the ribs and scapulae. However, the concept of an acoustic window[99] has allowed for effective ultrasound examination of the thorax in the presence of pleural pathology such as a pleural effusion or pulmonary consolidation or tumour abutting the pleura.

The normal thoracic ultrasound appearance is well described.[100–104] With the transducer held in the longitudinal plane, the ribs are visualised on ultrasound as repeating curvilinear structures with a posterior acoustic shadow (figure 5). The overlying muscle and fascia are represented by linear shadows of soft tissue echogenicity. The parietal and visceral pleura is usually visualised as a single echogenic line no more than 2 mm in width which 'slides' or 'glides' beneath the ribs with respiration when using a low-frequency transducer. Two separate lines can be visualised when using a high-frequency transducer. Normal aerated lung blocks the progression of sound waves and is characterised by a haphazard snowstorm appearance caused by reverberation artefact which diminishes in intensity with distance from the transducer. Comet-tail artefacts can also be seen due to imperfections within the pleura and are best seen at the lung bases. The diaphragms are bright curvilinear structures which move up and down with respiration. The liver and spleen are readily recognised by their characteristic ultrasound appearance below the right and left hemidiaphragm, respectively.

Abnormal thoracic ultrasound appearance

Pleural effusion

Ultrasound has a higher sensitivity in the detection of a pleural effusion than clinical examination or chest x-rays including a lateral decubitus film.[105] The ultrasound appearance of

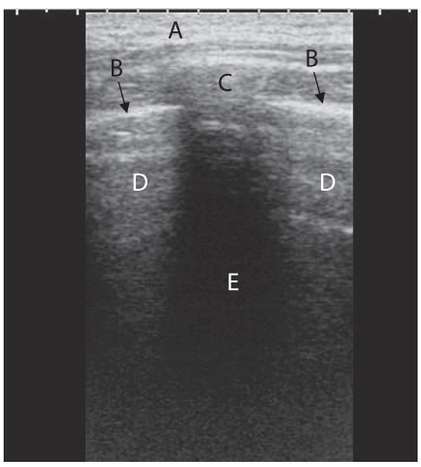

Figure 5 Normal lung with acoustic rib shadows: A, soft tissues; B, pleura; C, rib; D, normal lung; E, acoustic rib shadow.

a pleural effusion is an anechoic or hypoechoic area between the parietal and visceral pleura that changes shape with respiration (figure 6A).[106 107] Other sonographic characteristics of pleural fluid are swirling echo densities, flapping or swaying 'tongue-like' structures due to underlying compressive atelectasis of the lung and movable septae.[106] Depending upon its internal echogenicity and the presence of septations, a pleural effusion can be classified into anechoic if totally echo-free, complex non-septated if echogenic swirling densities are present, or complex septated if fine strands are present within the fluid (figure 6B).[103 108] Anechoic effusions can be either transudates or exudates, but complex effusions are always exudates.[103]

The volume of pleural fluid can be calculated using various formulae, but these are mainly applicable to patients receiving mechanical ventilation[109 110] and are difficult to apply in practice to non-ventilated patients. The following alternative classification has been suggested by Tsai *et al*[111]: (1) minimal if the echo-free space is within the costophrenic angle; (2) small if the echo-free space extends over the costophrenic angle but is still within a single probe range; (3) moderate if the echo-free space is between a one to two probe range; and (4) large if the space is bigger that a 2 probe range. Furthermore, a pleural effusion is usually considered too small to tap if it is <1 cm in depth.[106]

Pleural thickening

Occasionally a minimal pleural effusion can be hard to distinguish from pleural thickening which may manifest as an anechoic or hypoechoic stripe. The presence of a chaotic linear colour band between the visceral and parietal pleura using colour Doppler has a higher sensitivity for detecting pleural fluid than grey scale ultrasound alone and this is known as the 'fluid colour sign'.[112 113] However, the routine application and interpretation of this is likely to be beyond the expertise of the non-radiologist.

Malignant pleural effusion

Thoracic ultrasound can facilitate the diagnosis of a malignant pleural effusion. The presence of pleural or diaphragmatic thickening or nodularity[99 114] or an echogenic swirling pattern in patients with known malignancy[115] is highly suggestive of a malignant pleural effusion.

Pulmonary consolidation

Pulmonary consolidation is sonographically visible in the presence of adjacent pleural effusion acting as an acoustic window or if directly abutting the pleura (figure 7). It appears as a wedge-shaped irregular echogenic area with air or fluid bronchograms.[116 117] On colour Doppler ultrasound, branching tubular structures with colour flow is visible.[113]

Parapneumonic effusions and empyema

Parapneumonic effusions are usually hyperechoic with septae but can be hyperechoic without septae and even anechoic.[118] Ultrasound is better than CT at demonstrating septae.[118] However, CT is preferred in complex pleuroparenchymal disease as it is better at delineating the relationship between loculated pleural collections, parenchymal consolidation and the mediastinum.[119] The presence of septae does not imply loculations as the fluid may still be free flowing within the hemithorax.[118]

In a study of 36 patients with proven parapneumonic effusion or empyema, Kearney *et al* did not find any correlation between the ultrasound appearance and Light's stages of empyema, the presence of pus or the need for surgical intervention.[118] In contrast, two other studies have shown that septated parapneumonic effusions have a poorer outcome.[120 121] Chen *et al* showed that sonographically visible septations were associated with a longer hospital stay, longer chest tube drainage, higher likelihood of fibrinolytic therapy and surgical intervention[120] and Shankar *et al* found that a complex septated parapneumonic effusion had a 62.5% resolution rate with chest tube drainage compared with 81.5% with a complex non-septated parapneumonic effusion.[121]

Ongoing pleural infection despite adequate antibiotic therapy is often due to suboptimal placement of the chest drain, particularly in the presence of loculations.[122] Two studies have demonstrated the utility of ultrasound-guided chest drainage as the principal treatment for parapneumonic effusion or empyema with an overall success rate of 78%[121] and 72%.[80] Factors associated with failure were small-bore chest tube blockage, persistent pneumothorax or a pleural peel.[80]

Pneumothorax

The presence of a pneumothorax and hydropneumothorax can be inferred sonographically by the absence of pleural 'sliding' and the presence of reverberation artefact.[123 124] The utility of thoracic ultrasound for diagnosing a pneumothorax is limited in hospital practice due to the ready availability of chest x-rays and conflicting data from published reports. In a study of 53 patients following a transbronchial biopsy or chest drain removal, thoracic ultrasound using a high-frequency transducer and apical scans had a sensitivity and specificity of 100% for the detection of post-procedure pneumothorax compared with a chest x-ray or CT scan of the thorax.[124] An earlier report comparing ultrasound with CT scanning showed a lesser sensitivity following lung biopsy,[125] and a recently published report suggested that ultrasound was less sensitive and specific in patients with emphysema.[126]

Thoracic ultrasound technique

The technique for thoracic ultrasound is well described in several review articles[102 104 111] and by Koh *et al* in an online review article containing images and videos.[127] The patient should be positioned either in the sitting or lateral decubitus position if critically ill. The chest x-ray should be reviewed before the ultrasound examination.

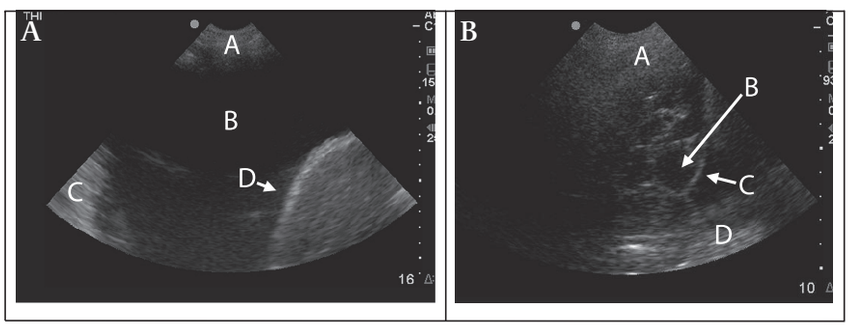

Figure 6 Pleural effusions. (A) Large anechoic pleural effusion: A, thoracic wall; B, pleural effusion; C, lung; D, diaphragm. (B) Loculated pleural effusion: A, thoracic wall; B, pleural fluid within a locule; C, wall of locule; D, lung.

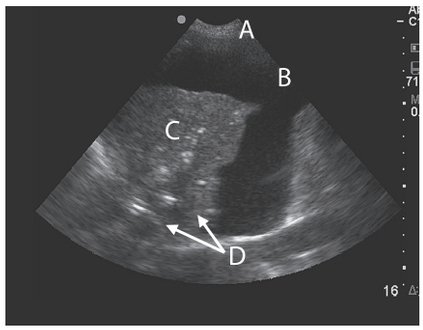

Figure 7 Lung consolidation with pleural effusion. A, thoracic wall; B, pleural effusion; C, consolidated lung; D, air bronchograms.

The ambient lighting should be reduced to maximise screen contrast. In general, a 3.5–5 MHz sector transducer provides good views of intrathoracic and upper abdominal structures including pleural fluid. A 5–10 MHz linear transducer should be selected for detailed examination of the pleura. Acoustic gel should be applied between the transducer and the area to be examined. The transducer should be held like a pen, applying firm pressure upon the skin to maximise acoustic coupling while resting the medial aspect of the palm upon the chest.

The image should be optimised by adjusting the depth, gain and focus. The depth should be adjusted until the area of interest fills the entire screen, while the gain should be increased or decreased to maximise the contrast between different tissues.

Examination should commence with the transducer placed within an interspace on the posterior chest wall on the side of interest. The transducer should be moved obliquely along the interspace (avoiding the acoustic shadow cause by reflection of the ultrasound by the ribs) in both the transverse and longitudinal planes, thereby minimising interference from the acoustic shadow from the ribs. It is imperative that the diaphragm is unequivocally identified before any invasive procedure to avoid inadvertent intra-abdominal penetration. The thorax should be examined posteriorly, laterally and anteriorly, particularly when a loculated pleural effusion is suspected.

The thorax should be examined using grey-scale real-time ultrasound, paying particularly attention to location, sonographic appearance and echogenicity.[111] The echogenicity of a lesion is defined relative to the liver which, by definition, is isoechoic. The contralateral thorax can be used as a control except where there is bilateral pleural pathology.

Ultrasound-guided pleural aspiration and chest drain insertion

The identification of a site for pleural aspiration using physical examination can be straightforward in the presence of a large free-flowing pleural effusion, but image guidance is recommended for all procedures as discussed above. When using ultrasound to select a site for aspiration of a pleural effusion, the site chosen should have (1) sufficient depth of pleural fluid (at least 10 mm), (2) no intervening lung at maximal inspiration and (3) minimal risk of puncture of other structures such as the heart, liver and spleen. It should be noted that ultrasound will not prevent inadvertent laceration of the intercostal neurovascular bundle, particularly where they run within the intercostal space medial to the angle of the rib.[24]

Once a site has been localised, it should be marked either with an indentation or indelible ink and a mental note made of the maximal depth of fluid present and the required angulation of needle insertion. It is preferable to perform the aspiration at the time of the ultrasound rather mark a spot for subsequent aspiration[20] as any alteration of the patient's position may significantly alter the relationship between the skin marker and the underlying pleural fluid.[20 21 102] Real-time guidance using a free-hand approach may be necessary in small or loculated pleural effusions.

The technique of ultrasound-guided chest drain insertion is similar to that for pleural aspiration. The main purpose of ultrasound is to identify a safe site for aspiration of fluid followed by insertion of the chest drain. The procedure is rarely performed under real-time guidance.

Pleural procedures within the critical care setting

- **Ultrasound guidance reduces the complications associated with pleural procedures in the critical care setting and its routine use is recommended. (C)**

Thoracic ultrasound within the critical care setting is especially useful due to the portability of the equipment when treating and diagnosing relatively immobile patients. Erect and, less commonly, decubitus chest x-rays are frequently used to diagnose pleural effusions. However, these views are rarely possible in critically ill patients. Diagnosis of pleural effusions on supine films is much more challenging and frequently inaccurate.[128] The use of bedside ultrasound by appropriately trained intensivists has been shown to safely identify and guide aspiration of pleural effusions in mechanically ventilated patients.[129] Of the 44 effusions that were aspirated during this study, the pleural effusion was not evident on a supine chest x-ray in 17 cases.

Ultrasound guidance is strongly recommended in this setting, not only because the diagnosis of pleural effusions is more difficult but also because the consequence of complications is often more serious. With ultrasound-guided procedures the complication rate is similar to procedures undertaken in other settings.[101 102]

Thoracic ultrasound training

- **At least level 1 competency is required to safely perform independent thoracic ultrasound. (✓)**

Thoracic ultrasound is a very operator-dependent procedure where imaging acquisition and interpretation are carried out simultaneously. There is little evidence to specify the length of training required for a non-radiologist to become competent in basic thoracic ultrasound.[130] In the UK the Royal College of Radiologists has published guidelines establishing the minimum standards required to achieve basic or level 1 competency in thoracic ultrasound.[131] Although the guideline defines a minimum number of supervised procedures, it should be recognised that some individuals may require more supervision to achieve competency in thoracic ultrasound. An additional 100 scans to achieve level 2 standard or 2 years further experience at level 1 standard would allow the individual to train others to level 1 thoracic ultrasound standard.

In practice, more scans are required beyond level 1 competency to achieve a reasonable level of expertise in thoracic ultrasound, particularly where there is loculated pleural fluid. It is advisable for the novice to start with patients with simple free-flowing pleural effusions before moving on to patients with complex pleural or pleuroparenchymal disease.[102] The images should be correlated with the CT scan of the thorax or advice should be sought from a radiologist if the individual is unable to interpret the acquired images.

Competing interests No member of the Guideline Group is aware of any competing interests.

Provenance and peer review The draft guideline was available for online public consultation (July/August 2009) and presented to the BTS Winter Meeting (December 2009). Feedback was invited from a range of stakeholder institutions (see Introduction). The draft guideline was reviewed by the BTS Standards of Care Committee (September 2009).

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